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A MANUAL OF VENEREAL DISEASES

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A MANUAL OF VENEREAL DISEASES

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Introduction by
Sir ALFRED KEOGH, K.C.B., late Director-General of the Army Medical Service.

History, Statistics, Invaliding, etc.,
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Clinical Pathology and Bacteriology,
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Clinical Course and Treatment,
Major C E. POLLOCK, R.A.M.C.

ROYAL ARMY MEDICAL COLLEGE
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SECOND EDITION

REVISED AND LARGELY RE-WRITTEN

With new matter by Major L. W. HARRISON, R.A.M.C., Clinical Pathologist, Military Hospital, Rochester Row.

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PREFACE TO THE SECOND EDITION

Since the publication of the first edition of this Manual, our knowledge of syphilis, its pathology and treatment, has made very great advances. This has necessitated the addition of much new matter and the revision of most of the former work. Major L. W. Harrison has practically re-written the chapters on the Pathology of Syphilis and has contributed fresh ones on the treatment of syphilis with salvarsan and neo-salvarsan, and also on the vaccine treatment of gonococcal infections; he is also responsible for the section dealing with the treatment of Gonorrhoea by the local application of heat.

While endeavouring to bring the Manual completely up-to-date, the editors have tried to include only such matter as should be really useful to those engaged in treating Venereal Diseases.

C. E. P.
L. W. H.

London,
April, 1913.

PREFACE TO THE FIRST EDITION

At the forty-eighth meeting of the Army Medical Advisory Board, on July 23, 1903, it was decided to appoint a Sub-Committee to consider the question of the treatment of Venereal Disease in the Army. This Committee collected information from a considerable number of sources, statistical and otherwise, and at the same time propounded a series of questions, on the subject chiefly of diagnosis and treatment, to various acknowledged experts in this country, and to medical officers of experience, who were known to have paid particular attention to the subject of Venereal Disease in the Army. At the same time Captain (now Major) C. E. Pollock, R.A.M.C., was deputed to visit various hospitals, both civil and military, on the Continent, with a view to collecting the latest intelligence as to the practice of experts abroad.

The answers of the various experts at home, and of the Army medical officers referred to above, were published in the second report of the Sub-Committee, and the information collected by Captain Pollock in the third report. The first report was mainly concerned with an analysis of statistics, and of the latest literature available on the subject. The Committee issued a final report on October 20, 1905, summarizing the information collected, and making many useful recommendations. The reports of this Sub-Committee must always remain a most valuable mine of information, and represent a great deal of work and investigation. It was felt, however, that the form in which they were issued was not one likely to appeal to the ordinary working Medical Officer, and at the

119th meeting of the Advisory Board, June 22, 1906, the suggestion was made that the information contained in these reports might be summarized, and placed in more readable form, so as to furnish medical officers of the Army, and others interested in the question, with a readily portable and convenient manual. At first it was thought that this might be managed by merely extracting from, and condensing the letterpress of the original reports, but it was soon found that this was impracticable. It was therefore decided that the suggested manual should be merely based on the reports, and be prefaced by a short introduction relating to the history of Venereal Diseases in the Army, with a short account of the latest knowledge on the subject of the *Spirochaeta pallida*, with especial reference to the best methods of microscopical investigation of the same. The general question of diagnosis and treatment has been entrusted to Major Pollock, who was very largely connected with the work of the Sub-Committee, while the subject of microscopical investigation has been undertaken by Major (Brevet Lieut.-Colonel) Leishman, R.A.M.C., Professor of Pathology at the Royal Army Medical College. At the same time I was instructed to undertake the general editorship, as well as the questions of History and Prevention.

The above sufficiently explains the genesis and object of this Manual. It is not intended as an exhaustive treatise, or to compete with any of the great systematic works, on the subject of Venereal Disease. It is intended merely to act as a convenient manual, for the use primarily of the Army Medical Officer, to assist him in his daily work in the prevention and treatment of Venereal Diseases.

Charles H. Melville, Lt.-Col. R.A.M.C.,
Secretary Army Medical Advisory Board.

INTRODUCTION

In selecting officers of the Army Medical Service to prepare a Manual of Venereal Diseases, the publishers have taken into consideration the vast amount of material available in the British Army for studying the subject. It is unfortunately true that British troops suffer from venereal disease to a much greater extent than most other armies; but it would be unfair to conclude from this that morality and physiological restraint are less prevalent amongst British than amongst foreign soldiers. The incidence of venereal disease in different countries depends upon causes which have little bearing upon the ethical aspect of the subject, although there is always a tendency, in dealing with it, to drag this aspect in. Statistics are especially misleading in this respect, and examples might be cited, which tend to show that in certain garrisons, where venereal diseases are least prevalent, the standard of public morality is lower than in neighbouring garrisons where the incidence is high.

Much prominence has been given to the influence of temperance on the notable decline of venereal disease amongst soldiers in the United Kingdom since 1884, but, although there is, no doubt, some connexion between intemperance and exposure to infection, much might be suggested to detract from the importance of this influence, just as, on the other hand, much might be suggested to prove a close connexion between the decline of venereal disease and the general raising of the standard of cleanliness amongst the class of women by whom the

infection is spread. The effect of wider knowledge, of better habitations, better water supplies, and better facilities for ablution and general cleanliness, on the gradual decline of venereal diseases in this country during the last quarter of a century, can scarcely be questioned; while to a lack of these essentials one must attribute the absence of any definite or progressive decline during the same period in garrisons in India and the Colonies, where the sanitary control of crowded bazaar populations is difficult and complicated. Venereal diseases are propagated, in fact, in filthy surroundings more than in cleanly surroundings, and it may be regarded as an axiom that the chances of avoiding infection are in direct proportion to the extent to which cleanliness and personal hygiene are practised by those who run the risk of infecting or of being infected.

The question of prevention of infection by legislative control of prostitution opens up too wide a field for consideration in a short introduction such as this; yet it cannot be passed over entirely in silence. There are many who, basing their assertions on certain statistical tables, declare that legislative control has not influenced the incidence of venereal disease one way or the other. But there can be no doubt that the low incidence of venereal disease in Continental armies is mainly due to systems of legislative control, and it is a significant fact that the two great Anglo-Saxon States, whose attitude in opposition to legislative control is similar, have a far higher incidence of venereal diseases in their armies than has any other country. Italy has proved by experiment the danger of removing this control and the advantage of restoring it; and we, too, are proving this in India and elsewhere. The heated discussions that have arisen to obscure the question depend more upon differences of opinion regarding the nature and morality of legislative control of prostitution than upon a denial of the scientific fact that the spread of an infectious or contagious disease, be it of venereal or other origin, can be and

is limited by such measures as notification, isolation, and adequate treatment.

Recent discoveries regarding the pathology of syphilis, and the improved methods of treatment now practised in the British Army, by which continuous treatment can be carried out easily and without loss of efficiency, add a special value to those portions of the manual which deal with this part of the subject. They lead the way to a field in which much useful work may be done by every one whose duties bring him in contact with this class of disease; and the knowledge, which they place in his hands, provides an equipment, that was previously lacking, for rational and scientific study.

ALFRED KEOGH.

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CHAPTER I

HISTORY: METHODS OF PREVENTION

"In the yeare of our Lorde 1494 in the moneth of December when Charles the French King tooke his journey into ye parts of Italie to recover the Kingdom of Naples, there appeared a certain disease throughout al Italie of an unknown nature which sundrie nations have called by sundrie names. The Frenchmen call it the disease of Naples, because the souldiers brought it from thence into Fraunce. The Neapolitans call it the French disease, for it appeared first when they came from Naples, and so other languages call it by other names, whereupon we need not greatly to passe, but rather what the true nature and cure thereof is." Thus begins the "Fifth booke of Maister John Vigo of Gennuai, of the French Pockes." I think the hint of the master may well be taken here, and that in a short manual like the present it would be out of place to dilate on the origin and history of Syphilis, whether it was, or was not, known to the Chinese in ancient days, whether it originated as above stated at Naples, or whether it was introduced by the sailors of Columbus on their return from America. But before proceeding to "passe to the true nature and cure thereof" it is necessary to say a few words on the history of Syphilis, and other Venereal Diseases in the British Army, during the latter part of the nineteenth century, and their effect on the total efficiency of the Army, as evidenced by the number of men reported "sick" daily from these causes, and the total loss to the Service due to them, as evidenced by their effect on

the invaliding rate, and also to touch on the question of prevention.

As a basis for this study, I propose to take the statistics furnished by the two largest and most homogeneous sections of the British Army, those, namely, which serve in the United Kingdom and in India respectively. This selection may seem somewhat arbitrary, but in the study of so complex a subject as the epidemiology of Venereal Disease, a question affected by so many side issues of ethics, and sociology, there is a distinct advantage in avoiding the many other influences, as of climate, surroundings, etc., which the inclusion of all the smaller garrisons scattered over the globe, some of them numerically quite unimportant, would introduce. I propose to limit my study to the period which has elapsed since 1880. This, again, may seem an undue limitation, but this period is one during which the Army has continuously been of the same composition as regards age of individuals, and terms of enlistment, throughout; and at the same time of a composition in these respects which it is likely to retain for as long a time as we can at present foresee.

To further simplify matters I have restricted the figures in the tables, and the curves on the plates attached, to those which refer only to Syphilis and Gonorrhoea, the two most important of the diseases of the class. Soft Chancre may be taken to vary pretty steadily with gonorrhoea. It is decidedly more important in India than in England, bearing to gonorrhoea, as regards the number of men constantly inefficient from each, a ratio of about one to four in the United Kingdom, and of slightly more than one to two in India. Its effect as a cause of invaliding is practically nil.

Appendix I and Chart I show, the former by the actual figures, the latter by graphic curves, the number of men constantly sick, and the number annually invalided, for syphilis and gonorrhoea, per 1,000 of strength of the troops stationed

in the United Kingdom, from 1880 to 1910 inclusive. The invaliding due to gonorrhoea is so small, never having in any one year in the period under review attained to 0·2 per 1,000, that its variations are not in my opinion of sufficient instructive value to merit their being graphically represented, the figures only therefore are given for this item. Taking the numbers constantly sick, it will be seen that both syphilis and gonorrhoea tended to increase during the earlier years of the third of a century with which we are concerned, up till 1884, in the case of the former disease, and up till 1886 in the case of the latter. From the above dates we have a steady and continuous fall in the average numbers constantly sick from both diseases, the fall being more marked and more rapid, as the antecedent rise was also more marked, in the case of syphilis than in that of gonorrhoea. Thus while syphilis in 1884, when at its greatest height, accounted for a daily inefficiency of over 13 per 1,000, gonorrhoea never attained to a higher figure than 7·05 per 1,000, in 1886. On the other hand, in 1910 both diseases having fallen to a very low figure, between 2 and 4 per 1,000, syphilis occupied a lower place, by 0·2 per 1,000, than the other member of the group. The fall in the number of men constantly sick from syphilis is remarkable, and not easy to account for. Probably there are a multiplicity of causes, but I have little doubt that increased temperance is by far the most important of all. In that case it may be said that the curves of syphilis, and gonorrhoea, should have maintained a more exact parallelism, since an indirect influence like temperance should affect both members of the group equally if at all. I offer the following explanation of this anomaly, as at least a possible one. Syphilis is probably in most cases contracted from the more degraded class of prostitutes, with whom an ordinarily self-respecting man does not consort when sober. The more respectable class of woman, when affected by this disease, will either seek treatment, or, frightened by her illness, abstain from further pro-

miscuous intercourse. Gonorrhoea, being in its earlier stages more painful, leads both classes of women to seek immediate treatment, which few of them probably persevere in beyond the stage of apparent cure. A woman of either class infected by this disease, therefore, will for a short time abstain from promiscuous intercourse, but once the initial severe symptoms are over will return to her former mode of life. If this explanation were the true one we would expect to see the two diseases continue to occupy their reversed position, and this, as the curves show, has been the case since the year 1900, with one exception. Even this exception might be twisted into an argument in favour of my theory, since it occurred in the year 1902, when so many troops returned from South Africa, and may be presumed to have been somewhat out of hand, in a moral sense. I do not, however, wish to labour the point unduly. The salient fact remains, that as temperance has increased, venereal disease has steadily diminished, and syphilis much more markedly so than gonorrhoea.

Whether we may expect from this cause alone any further great reduction of Venereal Disease under present social conditions is to be doubted. Amongst every 1,000 men there will be always some whose passions are so unbridled that they will indulge in promiscuous connexion at any risk, while there will be a larger number who will oscillate between discretion and promiscuity, according to their moral stability, this condition of moral stability depending largely on their sobriety at the time. It is this last class which can be most largely affected by the temperance movement, and as long as this continues to hold its present influence we may hope to see the total rate low, and the more severe disease less prevalent than the other, for reasons already stated. The question then arises whether in a population so largely composed of Teutonic and Scandinavian elements the temperance movement can ever progress beyond a certain extent. Its rapid success of late years, especially

amongst the young soldiers at home, does not necessarily point to an equally victorious career in the future, and in that case it is possible that we have reached, or at least approached, the zenith of temperance, and therewith the nadir of Venereal Diseases, in as far as they are conditioned by this influence. This is, however, verging on the question of prevention, which falls for treatment at a later stage.

The invaliding rate for syphilis shows no such marked fall as the curve of constantly sick. Since 1902 there has, however, been a steady fall, due primarily to the introduction of the continuous treatment of syphilis, with which the name of the late Colonel Lambkin is so honourably associated. In support of this it may be stated that in the Brigade of Guards, the treatment of the venereal sick of which was most directly under this officer's supervision, no men have been invalided for syphilis since the introduction of the continuous method in May, 1905.

The invaliding rate is, as the curve shows, very markedly lower in 1910 than it was in 1902 (0·28 per 1,000 as compared with 2·08); in this respect improvement is still to be hoped for.

Turning now to the Army of India, we find curves and figures markedly different from those which we have just been considering. Starting with comparatively low figures in 1880 (*see* Chart II and Table 2), we have in both diseases a strong upward tendency dating in the case of syphilis from the year 1888, in which the Contagious Diseases Act was abolished in India. In the case of both diseases the maximum number constantly sick was attained between 1894 and 1896, since when the fall has been rapid and continuous. This fall has in the main been due to the introduction of the Cantonment Act of 1897. The main features of this Act are as follows :—

(*a*) Establishment of Cantonment General Hospitals for the reception of cases of contagious disease, as well as for other diseases.

(*b*) Power to compulsorily examine and detain those suspected of suffering from such diseases.

(*c*) Power to exclude any persons from cantonments who do not comply with the provisions of the Act.

(*d*) Power to remove brothels and prostitutes.

(*e*) Exclusion of brothels and prostitutes from regimental bazaars.

(*f*) Prohibition of loitering and importuning.

Registration, compulsory examination otherwise than under (*b*), and jurisdiction outside cantonment limits, are not provided for.

Other causes which have co-operated are probably increased temperance, the personal influence of regimental and other officers, lectures on the advantages of temperance and continence by chaplains, medical officers, and regimental officers, the placing of dangerous places out of bounds, the prolonged continuous treatment of cases of syphilis out of hospital, encouragement of games, athletics and rational amusements in barracks, etc. In India, also, it may be noted that of late years syphilis has accounted for less inefficiency than has gonorrhoea. This is in part due to the fact that the treatment of cases outside barracks, which affects syphilis much more than gonorrhoea, has reduced the number of admissions to hospital due to a single infection. It is noteworthy, however, that in India as in England when Venereal Diseases have been in excess syphilis has taken the lead, when they have fallen gonorrhoea has come to the front. In India, as in England, I attribute this largely to an increased habit of temperance. Throughout the period under review the Army of India has suffered more from Venereal Disease than the Army serving in the United Kingdom. This may be attributed to the inevitable ennui of Indian life, the lower class of the women, and their greater venality, and also their greater lack of cleanliness.

The invaliding rate due to syphilis in the Army of India per 1,000 of strength, is given in Appendix I and Chart III. One is at once struck by the fact that these curves follow with remarkable parallelism the curves for the average constantly sick for this disease, the rise and fall being contemporaneous. The very marked difference here between the United Kingdom and India is very hard to explain. The relationship between the two sets of curves shown by the Indian figures is what one would expect and does not call for an explanation, that shown by the United Kingdom is paradoxical. The most feasible explanation would seem to be that the invaliding rate in the United Kingdom is to some extent affected by the invalids sent home for change from foreign stations. These men are usually after a certain period of furlough either permanently discharged the Service or posted to the depôt or home battalion. In the case of permanent discharge the fact would be recorded in the returns for the command from which the invalid came, but after he has returned to duty, any relapse of the disease resulting in permanent invaliding would be laid to the account of the United Kingdom. We can imagine, then, the invaliding for the United Kingdom being maintained at a steady rate by this gradual influx of cases from abroad. I have included a curve showing the numbers per 1,000 of strength invalided home for change, as well as those invalided direct out of the Service from India, with the combined curve showing the totals for both forms of invaliding. There is little to remark on except the accurate parallelism of the curves. The effect of the South African War on these figures is interesting. Evidently during its continuance medical officers were more chary of invaliding direct out of the Service, and more inclined to try the effect of change of climate first.

The main object, one might almost say the only justification, for the study of the history of any disease, is that such study may assist us in our struggle with that disease in the future.

This leads us at once to the question of the Prevention of Venereal Diseases, a subject which has a history, and a stormy one, of its own.

The history of the systematic Prevention of Venereal Disease in England may be said to begin with the Contagious Diseases Act of 1864. By this Act provision was made whereby at certain places detailed in the schedule of the Act, on an information, not on oath, laid before a justice of the peace, by a superintendent or inspector of police, or by any registered medical practitioner, stating that the informant "has good cause to believe" that "a certain woman" is a common prostitute, and has a contagious disease, and within fourteen days before the date of the information, "was in a public place within the limits of a place to which the Act applies—for the purposes of prostitution," the justice might call on that woman to appear to answer the charge, and "on oath being made before him substantiating the matter of the information to his satisfaction order such woman to be taken to a certified hospital for medical examination." The result of this examination was to be reported to the justice, and if the woman were found to be suffering from contagious disease the justice could issue an order for the detention of the woman for treatment for a period not exceeding three months.

The places to which the Act was made applicable were Portsmouth, Plymouth and Devonport, Woolwich, Chatham, Sheerness, Aldershot, Colchester, Shorncliffe, The Curragh, Cork, and Queenstown. The limits of these places were laid down with some liberality: Aldershot, for instance, extending as far as Pirbright, and even Eversley. This somewhat crude Act was repealed, and replaced, in 1866, by another Act which laid down that—

"Where an information on oath is laid before a justice by a superintendent of police, charging to the effect that the informant has good reason to believe that a woman therein named is

a common prostitute, and is either resident within the limits of any place to which this Act applies, or, being resident within five miles of those limits, has, within fourteen days before the laying of the information, been within those limits for the purpose of prostitution," the justice shall issue a notice calling on such woman to appear at a time and place laid down in the notice. If the woman appeared, in person or by proxy, or if she failed to appear (proof being given that the notice was served on her in due time to enable her to do so) the justice, if he thought the charge of prostitution substantiated, was empowered to order "that the woman be subject to a periodical medical examination for any period not exceeding one year, for the purpose of ascertaining at the time of each such examination whether she is affected with a contagious disease." The difference between these two Acts is worth noting. By the Act of 1864 the woman had to be charged with being both a prostitute and diseased. By the later Act the accusation of prostitution was held sufficient to carry the presumption of disease. This change is significant in its bearing on the inequality with which the two sexes are treated by almost all Contagious Disease legislation. This point will be referred to later. Provision was also made by this Act for the institution of "certified hospitals," the appointment of visiting surgeons and inspectors of hospitals, these details being left to be carried out by the Admiralty or the War Office. The stations selected were the same as those detailed above with the addition of Windsor.

In 1869 another Act was passed, adding the following places to those already mentioned, viz., Canterbury, Dover, Gravesend, Maidstone, Southampton and Winchester, and also extending the five mile limit mentioned in the Act of 1866 to one of ten miles, and also making the provisions of the Act applicable to any woman who, being "resident within ten miles of those limits, or having no settled place of abode, has within fourteen days before the laying of the information, either been

within those limits for the purpose of prostitution, or been outside of those limits for the purposes of prostitution in the company of men resident within those limits." In May, 1883, up till which time the above Acts were in full force, an order was issued abolishing the compulsory examination of women, and from that period until the Contagious Disease Repeal Act of 1886, by which the above-mentioned Acts were repealed, they existed in a state of suspended animation. Since the last named date there has been no renewal of them. The effect of these Acts is graphically shown in Appendix I, Chart IV, showing the admissions for all Venereal Diseases in fourteen stations under the Acts, and in fourteen other stations not under the Acts from 1860–1898.

The first thing that strikes one on looking at these two curves is their remarkable parallelism. In both curves we find a rise in 1867, less in the protected than in the unprotected stations. After 1869 the fall in the curve for unprotected stations is practically equal to that in the curve for protected stations, but the whole curve is throughout more irregular. Commencing in 1875 in the case of unprotected stations, and a year later in those classed as protected, we have a steady rise in both curves, the maxima being reached in 1883 in the former class and in 1884 in the latter. The repeal of the Acts in 1886 is followed by a distinct fall in the curve referring to previously protected stations, a simultaneous fall showing itself in the other curve also. The main lesson to be gathered from these curves appears to be that the rigorous application of repressive measures directed against women suspected of prostitution cannot abolish Venereal Diseases, nor even prevent their increase. The utmost that such measures can effect is to control the tide, as shown by the very much more marked regularity of the "protected" curve, when compared with the "unprotected" one. The actual ebb and flow of that tide are not due to the presence or absence of repressive measures, but to the opera-

tion of social causes lying much deeper than any mere police measures can hope to penetrate. The inherent vice of all such Acts as those above referred to is that they apply to one sex only, and that the less aggressive sexually of the two. It may be taken for granted that the number of men who lead irregular lives is considerably larger than that of the women who do the same. Taking all people who lead habitually irregular lives as possibly diseased, and the Acts of 1866 and 1869 assume this in the case of the woman, we have at the outset the fact that the measures above prescribed can only apply to less than one-half of the total number of the possibly diseased. But probably of that minority only a comparatively small proportion were actually caught in the mesh of the Acts. To quote from the final report of the Committee of the Advisory Board: "The isolation of a particular section of infected per-"sons, namely, of diseased prostitutes, cannot be considered "an ideal method of arresting the disease, while large numbers "of infected persons of both sexes remain free to spread the "contagion.

"It is noteworthy that in certain foreign countries where "the police supervision of prostitutes has been carried out "much more strictly than was ever attempted in the United "Kingdom, serious doubts are now expressed as to the efficacy "of legal restraint in arresting these contagious diseases.

"One of the most remarkable examples of diminution in "prevalence of a contagious disease is afforded by the history "of syphilis in Sweden during the past century. The main "factor in bringing about this diminution is considered by "Professor Welander of Stockholm to have been the effective "and, if necessary, gratuitous treatment afforded in hospitals "by the State to patients of both sexes without the stigma pro-"duced by police compulsion. The opinion of many competent "continental authorities is to the effect that the voluntary sub-"mission to treatment by infected persons of both sexes is

"more likely to diminish the prevalence of Venereal Disease "than the compulsory treatment by police regulation of a "special class only.

"Taking into consideration the present state of expert "opinion abroad, and the opposition certain to be raised in this "country should the re-enactment of a statute on the lines of "the Contagious Diseases Acts be proposed, the Committee "has come to the conclusion that, in the United Kingdom at "any rate, an attempt to grapple with the problem of venereal "disease by methods of compulsory isolation and treatment is "neither practicable nor expedient.

"Better results are likely to be obtained by the diffusion of "the knowledge of the serious consequences of these diseases, "and the provision of effective treatment for both sexes under "conditions to which no penal stigma is attached. If this con-"clusion is sound, the more necessary is it that trustworthy "methods of treatment should be thoroughly understood by "members of the medical profession, and rendered readily "available both in military and civilian practice."

In India the experience of the working of Contagious Diseases Acts has been somewhat different. It is true (*see* Chart II) that there was a marked rise in the admissions for all Venereal Diseases prior to the abolition of the Acts in 1888, but this abolition was followed by a very startling and serious aggravation of these diseases, until during the years 1894 to 1897 the number of admissions yearly, from this cause alone, amounted to half the strength of the garrison. This alarming state of affairs led to the New Cantonment Act of 1897, which was immediately followed by a rapid fall in the number of admissions. Still the fact remains that the original Act, though a severe one, did not stop the rise in the total number of admissions for Venereal Disease during the later years of its being in force. Whether, if the Act had been continued, the terrible incidence of the years 1894 to 1897 would have ever been

reached may be doubted, but we have no reason to say that a rise would not have occurred. On the other hand, the fall since 1897 has not been entirely due to the New Act. During the later months of that year, and throughout the earlier part of 1898, a large number of troops were engaged in active operations beyond the Frontier, or living under practically field service conditions close to it. During 1899 troops were moved to South Africa, and for the next three years the Army of India consisted of men of steadily increasing age, and steadily growing experience of the country. The temperance movement must also be taken into account. Since the beginning of the century the admissions for Venereal Disease have been persistently low, as compared with former years, and those for syphilis, latterly, lower in India even than in the Army at home. The most gratifying reduction has, however, been in the invaliding rate. In 1910 the number of men invalided out of the service was the same in India as in the United Kingdom, and about one twenty-fourth of what it was in 1897. Charts are appended giving the curves for admission for all Venereal Disease, for China and Straits Settlements, Gibraltar and Malta (the one for a time, the other constantly under a Contagious Diseases Act), and for Egypt. These are interesting, but do not merit detailed attention.

They all teach the same lesson, and that is, that the main fluctuations in the incidence of Venereal Diseases are independent of the presence or absence of repressive Acts, and that, dating from the middle of the '90's, there has been some other strong social influence in the Army (probably temperance) acting to reduce their prevalence; and this not in isolated commands only, but throughout the Army generally.

The following information as to the present position of the question of prevention on the continent, the measures adopted in various countries, and the prevalence of Venereal Diseases in certain Foreign Armies, is extracted from the Report of the Committee of the Advisory Board.

"The prophylaxis of Venereal Disease generally, but more "especially syphilis, is at present attracting considerable atten- "tion on the Continent. In Germany and France there already "exists legislation for the control of prostitution and the pre- "vention of the spread of venereal disease. The leading authori- "ties are not, however, satisfied that as much is being done as "is possible. Societies, consisting of members of the legal "and medical professions and others interested in the public "health, have been formed to consider the subject with a view "to concerted action. The German Society holds an annual "Congress, while the French one meets monthly.

"In France police regulations, which involve registration "and periodical examination, do not seem to be very success- "ful. This is ascribed to prevalence of clandestine prostitution.

"At the German Congress for the Prevention of Venereal "Disease, held at Frankfort, March, 1903, most speakers ex- "pressed dissatisfaction with the working of the present Ger- "man police regulations, which are much the same as the "French. At the same time the general opinion was that some "kind of restriction is necessary.

"The plan of 'Control Strassen' seemed to meet with a fair "amount of approval.

"Prussian law requires notification in the following cases :—

"(1) If the case is likely to be a source of venereal contagion, "e.g., secondary ulcers of the mouth among employés "in workshops, or poor people living in overcrowded "dwellings.

"(2) Civil doctors must inform the Commanding Officer "when treating soldiers for venereal disease.

"Recent congresses on the Prevention of Venereal Disease :—

"1. Congress for the prevention of syphilis in Russia.

"2. Discussion, British Medical Association meeting, 1899.

"3. First International Congress for the Prevention of "Venereal Disease, Brussels, 1899.

"4. Committee appointed by the Medical Society of New "York to inquire into the spread of Venereal Disease "and means of its prevention.

"5. Second International Congress, Brussels, 1902.

"6. First Congress of the Deutsche Gesellschaft zur Bekämp-"fung der Geschlechts Krankheiten, June, 1903.

"In the Russian Congress various proposals were adopted "for the Army, such as lectures to the men, keeping syphilitic "cases under observation, etc. All these have either been "adopted in the British Army already or are about to be so.

"At the Second International Congress, Brussels, the only "resolution adopted which affects the army was as follows:—

"No. III. That all conscripts joining a regiment be given "a short pamphlet describing the dangers of gonorrhoea and "syphilis. This is also to contain a note to the effect that the "date of an attack of venereal disease must be remembered in "order to correctly inform the medical officer of the fact, should "it be necessary later on; also a brief reference to the dangers "of alcoholic indulgence and of tubercular disease.

"This pamphlet to be kept by the man on his discharge from "the army.

"MEASURES ADOPTED FOR PROPHYLAXIS IN ARMIES.

"3. *Comparison of the incidence of Venereal Diseases in "European Armies.*

	Admissions per 1,000 of strength.				
	German.	French.	Austrian.	Italian.	British.
1886 to 1890 (average, annual)	27·1	51·1	65·3	94·3	212·4
In 1900[1]	17·8	37·2	59·8	89·7	93·4
[1] In 1909 the ratios were	19·3	23·04	64·8	56·8 (1904)	66·0

"Venereal Disease is prevalent in the Russian Army. In "1899, out of a strength of 1,013,435 men 34,228 were admitted "for this cause = 33·77 per 1,000.*

"In Warsaw lectures are given to the men instructing them "in the nature and dangers of Venereal Disease, also recom-"mending continence and advising them to report sick early.

"In the French Army the following rules have been "adopted:—

"I. Lectures to the men.

"II. Monthly examinations of the men in private.

"III. Secret register of syphilitics.

"IV. No punishment is awarded unless the disease is con-"cealed.

"V. Houses of diseased prostitutes are put out of bounds.

"The French colonial corps suffer severely from Venereal "Disease. In most French colonies there is no regulation of "prostitution, and where it does exist it is very inefficiently "carried out.

"In the United States Army in Cuba weekly inspections for "the detection of venereal disease were held. Those so suffer-"ing were treated in hospital, or as out-patients confined to "barracks."

It would not be proper to quit this part of our subject without suggesting, at least, the lines on which further progress in the Prevention of Venereal Disease may be hoped for. And, first, I would point out that the State is responsible for placing the young soldier in a sexually abnormal condition, particularly abnormal considering the early marriage age of the class he springs from. It is therefore not only to the advantage of the State, it is its manifest duty, that it should do all in its power to prevent the young soldier from falling into those habits of promiscuous incontinence to which his position renders him

* In 1910, out of a strength of 1,227,100 men, 56,454 were admitted for venereal disease = 47·4 per 1,000.

so liable. This duty it can of course only carry out through its officers. And in saying officers I do not limit the term to the officers of any one branch, or department. Every officer in the Service, regimental officer, medical officer, and chaplain, every officer who is responsible for the moral and physical welfare of the men, or who wishes to see full ranks instead of depleted ones, is equally interested. To begin with, as officers of the Army, we are concerned solely with the men; the women are outside of our purview. Now it appears to me that our work as regards the men may be divided into two parts. The first part is to influence the men towards continence. *Syphilis insontium* may occur undoubtedly, but is extremely rare, and it is safe to teach the young soldier that, if he lives a chaste life, his chances of contracting Venereal Disease are far less than those of his contracting smallpox. It may seem a counsel of perfection, and to a certain extent so it is. But it is a fact that there are a large number of men who do practise continence for considerable periods, namely, those who put themselves into serious training for athletics, and that they are physically all the better for doing so. Again, there is a considerable social class, the Quakers, amongst whom moral and sexual purity is highly estimated, and I believe syphilis is almost unknown amongst them. The counsel may be one of perfection, but it is not therefore one of impossibility. Next it should be pointed out to the young soldier that not only is continence possible, and healthful, but that incontinence, so far from being a sign of manliness, and a characteristic to be proud of, is a sign of weakness, and a thing to be ashamed of. Fortunately this feeling is already beginning to spread, and we may hope that in time it may be considered no more manly to be incontinent, than it is manly to get drunk. It is no question that the latter used once to be the general opinion of young men, and not so very many years ago. The former opinion still survives, though it is already less popular than it once used to be. Hav-

ing got thus far, the young soldier should next be told how he may best avoid the inevitable temptations to incontinence that attack the healthy male adult. The majority of soldiers are fond of athletics, and the performance and practice of these should be encouraged. This is a matter which, of course, comes more directly under the regimental officer than the medical officer, but to show the value of this means of avoiding disease, not only on account of its physical effect, but also on account of the healthy moral tone that it can induce, I quote here at some length from a series of five lectures delivered by Professor Erik Pontoppidan to the students at the University of Copenhagen on "What Venereal Diseases mean, and How to Prevent them."

"There is, further, another development from which I expect a better outlook for the present young generation in respect to sexual health, namely, the development of *physical exercise*. Nothing counteracts so strongly the irregularities of the imagination and sensual affections consequent upon a lazy, sedentary life, accompanied with over-feeding and luxury, than bodily exertion and methodical, pleasant physical exercise. It develops force of character and energy, which are useful for all purposes in life, and ability to act; in short, a well trained body is not compatible with drink or sexual excesses.

"We have taken our '*Idræt*' from the English sport, and it has, therefore, been of interest to me on visiting England, where the sport is a time-honoured institution, to examine the relation between it and the venereal diseases, particularly with regard to students.

"As everybody knows who has visited London and the big English towns, an unbridled, widespread and wholly uncontrolled prostitution is met with there, together with very deficient sanitary conditions in connexion therewith, especially amongst the lower classes. Even the English army is sadly infested with venereal diseases. These things are

evident, but I was told unanimously by doctors and people intimately acquainted with this subject that syphilis and other venereal diseases are not very frequent amongst students, or generally amongst young gentlemen of similar social position. The reason thereof was not on account of any moral superiority to the other classes. The explanation of the more fortunate position of these young men in that respect—in contrast to the students on the Continent—was unanimously attributed to the fact that it was not considered 'good form' amongst them, or generally admitted, to talk about women and sexual questions in the same way as, for instance, French *étudiants*, with whom *la femme* plays an important part in their lives. The young Englishmen, on the contrary, are intent on their sport, it occupies all their leisure and claims all their interest. We have, as I have said, taken our sport from England : may we also adopt the manly character and fine feelings of the 'true gentleman' towards everything vulgar and unclean !"

I have said so much on the subject of temperance and its great influence on the question of the prevention of Venereal Diseases when discussing the historical part of our subject, that it is unnecessary to return to it here. This, then, is the first part of a rational system of prevention, to teach the young soldier that continence is possible and healthful, and that it may be best attained by leading an active, temperate, clean thinking, clean talking life. The second part is to teach him the dangers of incontinence, and the possibilities of ill health that may result from a single false step. Thirdly and lastly, if in spite of all encouragement, assistance, advice and warning, the soldier persists in a course of life that renders him from time to time incapable of performing his duties, the powers of discipline may fairly be called in to punish him for so doing, as in the case of the analogous vice of drunkenness. It may be objected that in punishing a man for contracting Venereal Disease we are punishing him, not for committing a crime, but for

being so unfortunate as to be found out. But this objection applies to all discipline. We do not punish a man for drinking, but for being so unfortunate as not to be able to conceal the effects of drink. His comrade with a stronger head may drink much more and escape detection. So, too, one man may by incontinence expose himself repeatedly to the risk of infection, and escape, while his unfortunate comrade falls a victim to his first false step. This cannot be helped. Major Howell, R.A.M.C., in the Parkes Memorial Prize Essay for 1901, gives a series of suggestions with regard to disciplinary measures which I reproduce here, from the Report of the Committee of the Advisory Board.

(1) That no official notice be taken of the first venereal admission or of any admissions for secondary syphilis, but that for every subsequent admission for Venereal Disease a " V " to be entered on the man's Regimental Defaulter Sheet.

(2) That all guards and fatigues missed by a man being in hospital for venereal disease (excepting first admissions and secondary syphilis admissions) should be made up by the man on his discharge from hospital.

(3) That extra drills be imposed to regain the efficiency lost while in hospital.

(4) At home permanent passes, and in India shooting passes, not to be granted to men having many entries for venereal disease.

(5) The number of " V's " in a man's Defaulter Sheet to be taken into consideration by the man's commanding officer before promoting him, or assessing his character on discharge.

(6) Any man who has suffered from syphilis not to be granted permission to marry until he has had a full course of treatment for syphilis, and has been clear of an entry for syphilis for at least two years.

(7) Any man who has had no admission to hospital for an officially fixed period, say one year, should have his previous " V's " cancelled.

(8) Regiments showing an annual admission rate for venereal disease much in excess of the average admission ratio for the whole Army should be debarred from proceeding on active service till all regiments showing less than the average rate have proceeded to the front, and even then should, if possible, only be employed on the lines of communication.

The difficulty with all such disciplinary measures is, of course, the risk of their leading to concealment of disease. I would be inclined therefore to allow a man to have two primary attacks of Venereal Disease without making more than a Company Entry. The third primary attack should be made a Regimental Entry. The making up of lost duties is a practical idea. The hardened sinner would know quite well that the longer he stayed out of hospital concealing his disease, the longer he would probably have to remain in hospital for recovery, and the more guards, etc., he would have to make up. Particular notice should, I think, be taken of any man who, while under treatment out of hospital for secondary syphilis, was found to have contracted gonorrhoea or soft chancre. The Committee of the Advisory Board also suggested for consideration the publication of an Annual Return showing the incidence of Venereal Disease by units of the Army, and there is much to be said for this. So also for the system adopted by Lieut.-Gen. Goodenough of calling for monthly returns of admissions for Venereal Disease by companies. In all such, however, only primary admissions should be noted.

The essence of the system that I suggest is that we should begin by placing a high ideal before the soldier as at least possible of attainment. I do not consider it a valid objection to say that the ideal is too high. We all know that the higher you

place your ideal the higher you are likely to attain, and this ideal is attained by many men over prolonged periods, and by some men maintained until marriage. All other systems of prevention accept incontinence as a necessary part of male life, and aim at making it safe. They place the ideal, if it can in any way be called an ideal, as low as possible, the figures prove that they fail to in any way attain to their ideal, that is absolute safety. To use a now historical phrase, "They put their money on the wrong horse." Let us at least try the high ideal, and instead of saying that incontinence is a necessity, say that continence is possible, and the best policy in the long run. We need never hope for absolute success, or to get an Army of Galahads, but we shall have the satisfaction of knowing that every diminution in the rate of Admissions for Venereal Disease means not only so many more healthy men in the ranks, but so many more men who have learnt the virtue of self-restraint, and thereby benefited not only their bodies, but their characters. Human nature being what it is, we must still have recourse to fear, and the danger of possible ill consequences, to keep men in the narrow path, and in the last resort the scourge of discipline to drive those that will neither lead nor be led therein; but the high ideal should come first.

CHAPTER II

SYPHILIS: DEFINITION—PATHOLOGY

Definition.—Syphilis is an infective disease usually acquired during coitus; the *Spirochaeta pallida* gaining entrance through a minute abrasion in the mucous membrane of the glans or adjoining skin of the penis. A general infection of the system takes place within a few hours; unfortunately, however, the clinical signs of this do not show themselves till some weeks have elapsed, and even then are not always definite. The chief and most objectionable characteristic of the disease, however, is its tendency to recur after long intervals of perfect freedom, suddenly attacking the central nervous system or some important organ, and leading to a rapid breakdown of the general system.

The Spirochaeta Pallida.—In view of the very general acceptance which has been accorded to the micro-organism discovered in syphilitic lesions by Schaudinn and Hoffmann, it has been thought well to devote to it a separate chapter.

There is no need for an exhaustive account of the various micro-organisms which, at one time or another, have been found in syphilitic lesions and suggested by their discoverers as the actual cause of the disease. There have been some twenty-five of these brought to notice in the last twenty years, but few have met with any degree of support or confirmation, and most have been speedily forgotten. The bacillus of Lustgarten is almost the only one which survived its discovery, in 1884, and succeeded in holding the field until

the suspicions as to its identity with the Smegma bacillus grew too strong for its further acceptance. Ten years later, Van Niessen discovered an organism closely resembling the Diphtheria bacillus, which met with some degree of support, but was finally discredited and, with the possible exception of the protozoon described by Schüller, no others have left any permanent mark on the history of the subject. It was, however, generally thought by bacteriologists that the disease was of bacterial or of protozoal nature, and that the failure to detect the germ was due either to faulty technique or to the fact that it might be of ultra-microscopic size.

The problem stood in this unsolved condition in April, 1905, when Schaudinn and Hoffmann announced, in somewhat guarded language, their discovery of the spirochete which is the subject of the present chapter. It is not the least remarkable feature of this discovery that it should have been accepted so soon and so generally by those best qualified to judge; this, no doubt, was in part due to the high esteem in which the work of the late Dr. Schaudinn was justly held, but, probably in greater part to the fact that the spirochete, whose presence in primary and secondary lesions was recognized on all hands, was of such a nature that it could readily be distinguished from others. Its non-recognition up to this time was also easily accounted for by the fact that special staining methods were necessary for its detection and that such methods had only been available of recent years.

While the constancy of its occurrence in the primary and secondary lesions was soon recognized, the actual proofs of its causative rôle were, of course, still lacking, but the evidence in favour of its being the cause of syphilis has since accumulated with great rapidity. It has been found in every type of syphilitic lesion, but never in those of other diseases, and the inoculation of animals with material containing

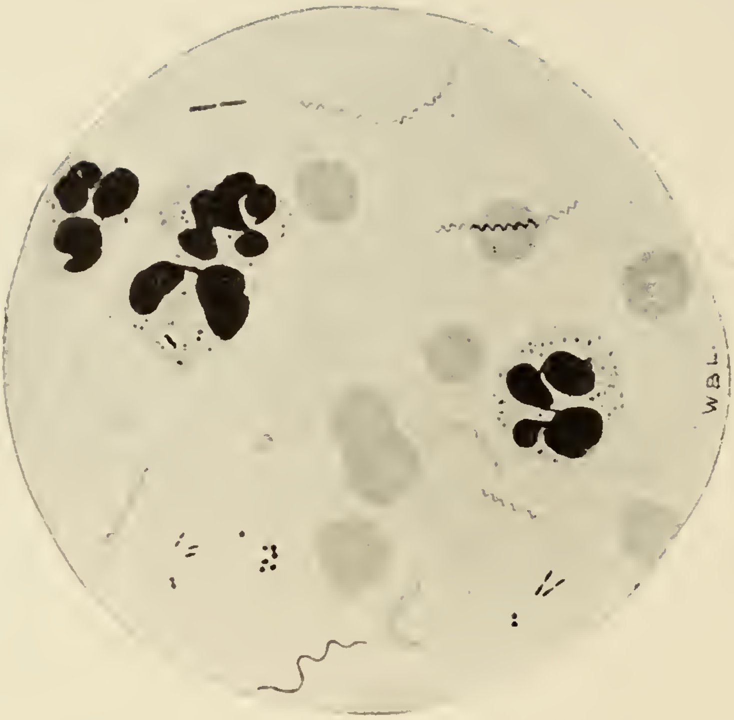

PLATE IIA.—Film preparation from a Condyloma; showing several examples of *Spirochaeta pallida* and one of *Spirochaeta refringens*.
Stained by Leishman's stain—method No. 2—and drawn with Zeiss's camera lucida. Zeiss apochromatic 2 mm. objective and No. 6 compensating ocular. Tube length, 160 mm.

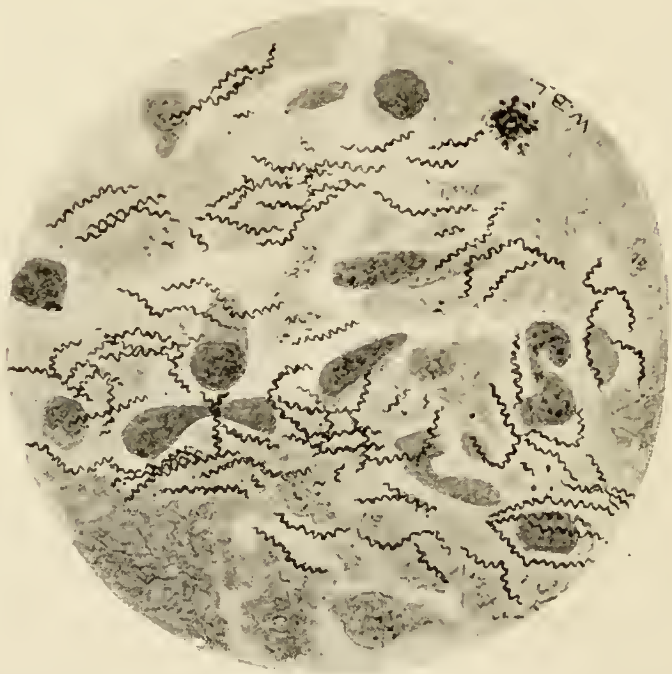

PLATE IIB.—Section of Spleen from a syphilitic foetus.
Stained by Levaditi's method No. 1, and drawn with Zeiss's camera lucida. Zeiss apochromatic 1·5 mm. objective and No. 6 compensating ocular. Tube length, 145 mm.

[To face p. 25.

PLATE II.]

the *Spirochaeta pallida* results in the formation of typical syphilitic lesions in which these organisms are constantly present. Altogether, therefore, although it still requires the successful inoculation of man with pure cultures to complete the chain of evidence, nobody now doubts that the *Spirochaeta pallida* is the cause of syphilis, or the conclusive evidence afforded by its presence in any suspected lesion. Within the past two years Noguchi and others have claimed on very strong grounds to have grown it in pure culture and to have produced typical syphilitic lesions in animals by inoculating them with these cultures.

For reasons connected with the biological position of the spirochete, into which it is unnecessary to enter, it was thought necessary to create for it a new Genus, and, for this purpose, Vuillemin suggested the name of *Spironema* in place of that of *Spirochaeta*. Schaudinn accepted this name, but, as it was found that it had already been employed in another connexion, he suggested in its place that of *Treponema*. By this last name, *Treponema pallidum*, the organism is now correctly known, but the older designation of *Spirochaeta pallida* is in more common use and will be adhered to in the present instance. Such a procedure may be further excused since it is far from improbable that fresh light may be thrown on the biological position of the parasite, which might necessitate yet another change in the generic name.

Description.—The *Spirochaeta pallida* is an extremely delicate, thread-like organism, spirally twisted and presenting several points by which it may be distinguished, with comparative ease, from other spirochetes. The chief of these points are its extreme tenuity, the regularity and close twisting of the spirals, its weak staining affinities and its low refrangibility. In the fresh, unstained condition, it may be seen in the hanging-drop, but this demands the best optical conditions and considerable proficiency in high-power

microscopy. It can be seen in the living condition much more easily by means of the dark-ground illumination (see p. 59), and this is the method by which it is now most frequently demonstrated.

When examined by this method it is seen to be actively motile, its movements being of four kinds: (*a*) rotation on its long axis, (*b*) bending and lashing, (*c*) contraction and extension of its spirals, and (*d*) slow progression. All of these are very characteristic of the *Sp. pallida*, and it will frequently betray its presence to a trained observer by its slow progression and wonderful flexibility before it has been brought properly into focus. It may bend to form an irregular circle, or an L, or, keeping the greater part of its axis straight, may form a loop of the last few microns of its length; save *Sp. pertenuis*, no other spirochete can compare with it in flexibility. On account of its slow rate of progression it is quite easy to keep the same specimen in the microscopic field for many hours together, and here again it differs from many other spirochetes, which move more rapidly across the field. Another point of some value in the recognition of *Sp. pallida* is its dead-white appearance under dark-ground illumination, when viewed with an oil-immersion or a dry apochromatic objective. To appreciate this point it should be examined in the same field with such spirochetes as *Sp. gracilis*, which the beginner, relying on a book description, may easily mistake for *Sp. pallida*. A good plan is to prepare a specimen from a chancre which is also associated with balanitis without taking any precautions to prevent the chancre exudate from becoming contaminated with the balanitic secretion. Such a specimen contains, besides *pallida*, multitudes of other spirochetes, some of them very fine and with closely set spirals, but it will be noticed that, amongst other differences, while *pallida* is dead-white other spirochetes are glistening. If the fine adjust-

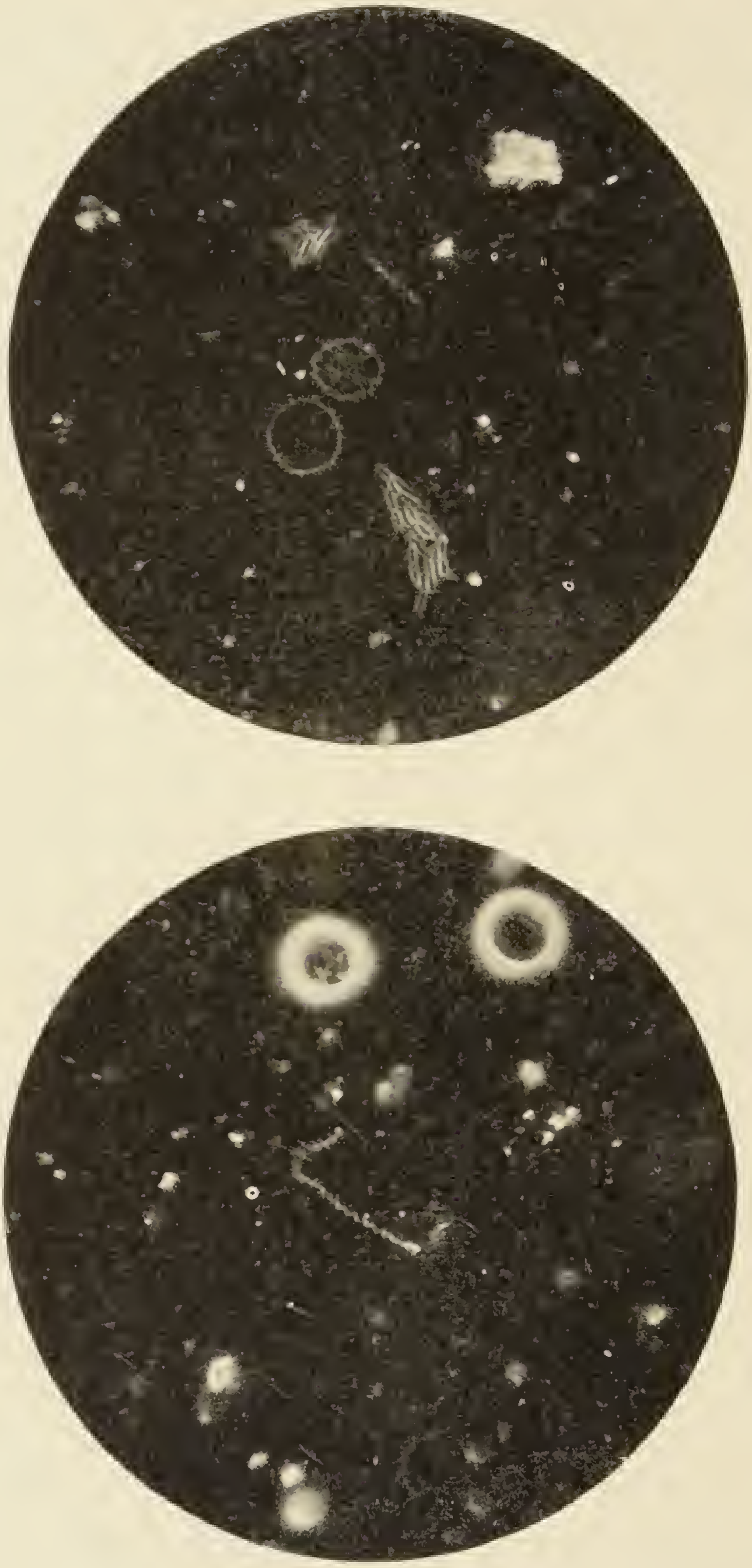

PLATE I.—Micro-photograph of living Spirochaeta Pallida, under dark ground illumination with Leitz concentric condenser, magnified 850 diameters. Taken by Mr. Ogilvy.

[To face p. 27.

ment of the microscope be moved the very least amount, so as to focus on a very slightly higher level, all other spirochetes which may be associated with *pallida* have a reddish tinge. Probably this is because pallida reflects all the light which strikes it, while other spirochetes, being thicker and consequently having a surface which is less steeply curved, pass some of the rays of light and break them up. Its hair-like tenuity, the regularity, depth and close twisting of its curves, are particularly well seen in the living organism, though these characteristics are well maintained in stained specimens. Its thickness has been estimated at $\frac{1}{4}\mu$ and its length varies from 4–24μ, being generally 7–10μ. The width of the curves, that is the distance from the summit of one convexity to that of the next, is very constant, 1 to 1·2 microns. This is a figure that is rarely departed from and is worth bearing in mind, as it is a point by which *pallida* may be distinguished from *Sp. refringens* and others which are often encountered in suspected material. In the absence of a micrometer, these curves may be measured, with approximate accuracy, by contrasting them with the diameter of a red blood corpuscle, if any happen to be in the field; remembering that the average diameter of a red cell is 7·5 microns, it will be seen that the spirochete, in this distance, will have made from six to seven turns (Plate I). In this manner the average width of the spirals can be ascertained with a fair degree of accuracy. If, however, an eye-piece micrometer is available, the value of whose divisions has been ascertained for the particular combination of lenses in use, the average measurement of the curves may be determined by taking the length of the spirochete in microns, counting the total number of the curves and dividing the former figure by the latter.

In stained preparations the *Sp. pallida* characteristically maintains the regularity of its spiral formation, a point of

distinction from many other spirochetes with which it may be associated in suspected material. Irregular forms are often seen, however, in film preparations. Sometimes it appears as a delicate helical spring which has been overstrained in one portion of its length and a few of its spirals straightened out, and sometimes curved forms, loops, figures of eight and irregularly twisted spirochetes are seen. I have never seen such atypical forms in living preparations, and conclude that these irregularities must be produced artificially in spreading the film, or the spirochete was engaged in one of the bending movements already described when fixed in position by the drying of the film.

As regards the relation of the spirochetes to the other elements found in living and film preparations, they are almost always free and not intra-cellular; at times, one may be seen apparently attached to a red blood corpuscle, while others are seen overlying either red cells or leucocytes, but I have never observed definite phagocytosis, and the occurrence of true intra-corpuscular forms, although reported in the early days of the discovery, has not been confirmed. At the same time there is good evidence that phagocytosis does occur in the tissues, as will be mentioned in the section dealing with the distribution of the parasite.

Great interest attaches to the finer details of the structure of *Sp. pallida*, but on this point there is no general agreement. Observers who have worked at this problem record very different results, the facts on the one hand pointing to the bacterial nature of the parasite, on the other to its being a protozoon. It would be out of place to go into this question at length, and it will suffice to indicate the principal features that have been described, leaving on one side any attempt to reconcile the conflicting views. Schaudinn himself was decidedly of the opinion that the parasite was a protozoon closely allied though not belonging to the *Trypanosomata*.

He was unable to make out any evidence of an undulating membrane, such as he had found in some other spirochetes, but he described and figured a delicate terminal flagellum, about half as long as the spirochete itself and sometimes bifid, a fact which he thought suggestive as to the possibility of longitudinal division. This flagellum could only be demonstrated by means of special flagellar stains—Loeffler's was the one with which he worked—and was not visible in specimens stained by Romanowsky's method. Schaudinn's observation has been confirmed by several others, though opinion is not unanimous as to the nature of these delicate little terminal threads, some regarding them as simple prolongations of the body of the spirochete. I have not, myself, been able to recognize this flagellum, though at times forms are met with in which one end appears to be extremely attenuated and not unlike the structure figured by Schaudinn.

The existence of a nucleus is uncertain. Schaudinn believed that the nuclear substance was diffuse, extending as a thread of chromatin throughout the length of the spirochete. Some workers have, however, described dots in the threads, either as dark-staining bodies or as light unstained areas, and Noguchi has described and figured in cultivated spirochetes spore-like bodies which take the chromatin stain.

Multiplication.—On this point there is also a divergence of opinion. While the majority hold that multiplication takes place by transverse division, such as occurs in all bacteria, others consider that longitudinal division is the rule. It is, once more, the much-debated problem of the bacterial or protozoal nature of the pathogenic spirochetes. Forms may be observed in preparations which lend support to either view. On the one hand, long spirochetes may often be seen presenting a constriction at or about the middle, an appear-

ance of thinning and stretching which, if carried further, would certainly end in the separation of the spirochete into two new individuals. Similar forms are readily recognizable in the larger spirochetes, such as those of relapsing fever and tick fever, but we get little help from this fact, as the same difference of opinion as to their interpretation exists here, although we have the assurance of several observers that they have seen transverse fission occur in spirochetes watched in living preparations. The varying lengths of different *Sp. pallida* supports the view that multiplication occurs by transverse fission. On the other hand, one often encounters forms which it is hard to believe are not stages of longitudinal division. Two spirochetes closely entwined are, of course, capable of being interpreted either as evidence of recent longitudinal cleavage or as being due to a mere entanglement of two free individuals, but forms which show an appearance of thickening at one extremity while the other is prolonged into two distinct spirals are not so easily dismissed. Such forms are only rarely to be seen, but are very suggestive of longitudinal division ; the minute size of the organism, even under the most powerful magnifications, must, however, be borne in mind and it is extremely easy to deceive oneself in endeavouring to interpret morphological details, such as this.

The method of multiplication of the *Sp. pallida* has been a subject of great discussion by the two schools which dispute as to its biological position ; those who maintain that it is a bacterium found their belief largely on its alleged transverse division, while the opposite school, which holds that it is a protozoon, assert in support of their view that it divides longitudinally. Metchnikoff and others have shown, however, that some bacteria divide longitudinally.

The biological position of the *Sp. pallida* is by no means settled. If it were proved that in some stage of its life

history it assumed "a resting form," it would strongly support its protozoal nature. Leishman has shown in the case of *Sp. duttoni* that a developmental form does exist, while Balfour and O'Farrell have demonstrated by means of the dark-ground illumination that the *Sp. pallida* sheds highly refractile granules at some stage in its life history, especially under the influence of salvarsan, and believe that these granules are possibly spore forms. The exact relation of the granules to the *Sp. pallida*, however, has not yet been demonstrated. The round spore-like chromatin bodies which Noguchi has described and figured in his cultivated spirochetes are interesting in this connexion.

This question of the biological position of *Sp. pallida*, however interesting to those engaged in its investigation, would lead us too far from the purpose of this chapter, but it is one of greatest moment in the further extension of our knowledge of the exact relationship of the parasite to the disease. Proof of the existence of a "resting form" of the spirochete would clear up many of the difficulties with which the subject is beset and might afford the solution of the problem as to the connexion between the spirochete and the later manifestations of syphilis.

Cultivation.—For some years the *Sp. pallida* resisted all attempts at artificial cultivation. In 1909, however, Schereschewsky claimed to have obtained impure cultures in inspissated horse serum. His observations were not confirmed at first, other observers, notably Levaditi and Stanesco, holding that Schereschewsky's spirochetes were thicker than *pallida* and non-virulent.

In 1911 Noguchi succeeded in obtaining pure cultures with which he produced typical syphilitic lesions in rabbits. He first obtained an impure culture by inoculating, with syphilitic rabbit's testicle, serum water (sheep, horse or rabbit serum 1, distilled water 3), to which was added a small

piece of fresh sterile rabbit kidney or testicle. The advantage of using syphilitic rabbit's testicle consists in its being almost free from other organisms and very rich in spirochetes. The culture was incubated at 37° C. under very strictly anaerobic conditions. The resulting impure culture of *Spirochaeta pallida* was freed from associated bacteria by taking advantage of the facts that *Sp. pallida* will grow through a Berkfeld filter more quickly than other organisms and will also penetrate further into the surrounding culture medium. After becoming accustomed to artificial conditions the spirochetes were induced to grow in serum agar to which a piece of sterile rabbit's kidney or testicle had been added.

Subsequently Noguchi obtained cultures directly from human lesions by inoculating deep ascitic or hydrocele agar stabs (2 per cent. slightly alkaline agar, 2 ; ascitic fluid, 1 ; total in tube, 15 c.c.), at the bottom of which was placed a piece of sterile rabbit's tissue. The material for inoculation is received into sterile saline in 1 per cent. citrate of soda and cut into small pieces. One of these is pushed to the bottom of each tube, while into the same tube are forced several drops of an emulsion of the syphilitic material. Some sterile paraffin oil is poured on the top of the medium, and the tubes are incubated at 37°C. under strictly anaerobic conditions. After two to three weeks the now putrefactive culture is examined by dark-ground illumination and if *Sp. pallida* is found some of the growth is carried to the bottom of more ascitic agar stabs by means of a capillary pipette, taking care not to split the medium. After two or three weeks *Sp. pallida* is found to have grown out into the medium as a faint hazy growth. The upper surface of the column of medium is sterilized with sublimate alcohol, which is poured away, and the tube is broken at its middle with a diamond and the application of a red-hot glass rod. The upper half of the tube is removed, leaving the cylinder

of medium standing up. The surface of this is sterilized and the cylinder gently broken across so as to expose some of the hazy growth. A little of this is picked up with a capillary pipette and inoculated into a number of other stabs; by repeating the process two or three times other micro-organisms are gradually left behind. By a very ingenious but simple method [1] the culture is induced to grow in a fluid medium.

With his cultures Noguchi claims to have produced typical syphilitic lesions in rabbits and monkeys. His "luetin," prepared from cultures of *Sp. pallida*, when injected into the cutis vera produces in some syphilitic patients skin lesions which are analogous to the reaction obtained in tubercular subjects by the similar use of tuberculin, and animals which have been inoculated with cultures of human *pallida* develop in their blood-serum substances which have the property of binding complement when incubated with antigen prepared from syphilitic rabbit's testicle.

Levaditi and Danulesco do not believe that Noguchi's spirochetes are *pallida*, because they have been unable to grow *Sp. pallida* by his method, and in one of Noguchi's own cultures which they received the spirochetes were not typical, conforming more to the characteristics of *Sp. gracilis*, besides being non-pathogenic for animals. These objections do not appear very valid, since, as Noguchi previously pointed out, pallida will change its morphological characters under adverse conditions of culture, and it is also quite easy to imagine that such a micro-organism could easily become non-pathogenic under artificial conditions.

Other workers, notably Sowade, Schereschewsky, Hoffmann, and Nakano claim to have obtained pure cultures by methods which are rather simpler than those of Noguchi.

[1] H. Noguchi: "A method for cultivating T. pallidum in fluid media." *Journal Experimental Medicine*, vol. xvi, 1912.

Briefly, these workers first obtain impure cultures by inoculating with pieces of syphilitic papule, chancre, or condyloma, horse serum which has been sterilized by heating at 58°C. for four hours on each of four days and then made gelatinous by raising its temperature very gradually to 65°C. or 70°C. To isolate the spirochete from banal organisms Nakano inoculates with the impure culture inspissated horse serum contained in a small Reichel filter, which, in turn, is surrounded by inspissated horse serum. The spirochetes are the first micro-organisms to grow through the filter and subcultures are made as soon as the growth appears in the medium outside. Sowade and Schereschewsky depend on the fact already mentioned that *Sp. pallida* grows faster into the surrounding medium than other organisms. The medium becomes liquefied around the contaminating organisms, but beyond this, in the solid medium, is the milky-white growth of *Sp. pallida.* When liquefaction has well advanced (about the fourth day) 70 per cent. alcohol is run along the canal of inoculation to the syphilitic material. This destroys the banal organisms. After ten minutes the alcohol is replaced by sterile distilled water and this again by sterile paraffin oil. The *Spirochaeta pallida* having grown into the medium beyond the area of liquefaction is not touched by the alcohol. To make subcultures the outside of the tube is carefully sterilized and it is then broken across below the upper level of the growth. The medium is cut across with a sterile knife. A specimen is taken from the situation of the growth and examined under dark-ground illumination. If found to be swarming with spirochetes the subculture is made. One or two subcultures may have to be made before cultures are obtained which are free from other organisms.

Animal Experiments.—For long, nothing but failure attended all attempts to infect the lower animals by inoculation of syphilitic material and it was not until 1903 that

Metchnikoff and Roux succeeded in infecting a chimpanzee with material derived from a chancre of one month's duration. Their work has been fully confirmed by many others, and we owe a large proportion of the recent advances in our knowledge of syphilis to experiments upon monkeys, and, as will be seen, upon rabbits.

In regard to monkeys, the reactions differ according to the species employed in the experiment; in the case of the higher, anthropoid apes, inoculation of the human virus is followed, after an incubation period which varies from 15 to 60 days, by a typical chancre which becomes indurated and presents all the characters of the Hunterian sore. This is followed by the appearance of secondary symptoms, induration of the glands throughout the body, syphilides of various types, papular or ulcerated, mucous patches in the mouth, alopecia and scaly syphilides on the palms of the hands. The closest resemblance to the picture of the disease in man is presented by the chimpanzee, but in no instance has the disease progressed beyond the secondary stage; tertiary symptoms have never been observed. In the lower monkeys, such as *Macacus rhesus*, *cercopithecus*, etc., the resistance to infection is higher and the disease usually goes no further than the primary sore which develops at the site of inoculation. The specific nature of the disease in monkeys was established, not only by the similarity of the symptoms to those in man, but by the fact that the disease could be successfully transferred from one animal to another for many generations, the type of the disease being similar in all cases. It was further found that, once an animal had recovered from the effects of the inoculation—and death rarely ensues except in the case of very extensive ulcerations—it was rendered immune to inoculation with fresh syphilitic material. The histological characters of the lesions proved to be identical with those of the same lesions in human syphilis.

As soon as the discovery of Schaudinn and Hoffmann was announced, the lesions of monkeys infected with this experimental syphilis were searched for the *Spirochaeta pallida* with positive results, not only in the primary sore but in the indurated glands and in the other manifestations of the secondary process; similar results were obtained in the case of monkeys inoculated with material which had been "passaged" through other monkeys. The application of the silver method of section staining to the tissues demonstrated, also, that the spirochetes bore the same relations to the various tissue elements as those found in the lesions of human syphilis.

In the case of the lower monkeys, such as *Macacus cynomolgus*, only the primary sore is produced, though Neisser has shown by inoculating other monkeys with the internal organs of these infected animals that the disease may be generalized. As a rule, induration does not follow, but the specific nature of the lesion has been established both by the results of successive inoculations from monkey to monkey and by the discovery of *Sp. pallida* in the lesions. In this case the best procedure is to scarify the free margin of an eyelid and to inoculate the virus by rubbing the material well into the scarified point. This site has been selected on account of its comparative freedom from the risks of secondary contamination and accident. After an incubation period which averages 23 days, a papule results at the site of inoculation which, in its histological characters, resembles the early stage of a human chancre. By observing due precautions as to technique, a positive result is almost sure to be obtained on the inoculation of fresh material from either primary or secondary human sources. Thibierge and Ravaut report that they succeeded in every case by employing this procedure, and they regard the absence of induration in the sore as being due to the freedom from the results of secondary infection.

It need hardly be added that numerous control experiments have been carried out by inoculating material derived from other sources and the secretions from the genital organs in non-syphilitic conditions; in no instance did the characteristic lesion result unless the inoculated material was derived from a case of syphilis.

It was natural that advantage should be taken of those successful experiments to investigate the infectivity of the various stages and lesions of syphilis and the association of the disease with the *Spirochaeta pallida*. Such experimental work is now going on extensively and has already yielded valuable results. It was, for instance, by means of monkey inoculations that Finger and Landsteiner demonstrated the infectivity of the sperm of a man whose secondary eruption was subsiding. Again, Buschke and Fischer proved the infectivity of material taken from malignant, ulcerated syphilides and, also, from an ulcerated gumma, 17 years after infection; the spirochetes were not found beforehand in these cases, and Buschke and Fischer suggest that this may have been due either to their being present in very small numbers or to their having assumed another form. Similarly, inoculation of blood suspected to be infective has, in the hands of Hoffmann, given positive results. In this instance the blood was derived from an infection of six months' duration and was taken from a vein in the arm; the *macacus* inoculated with this blood developed a chancre 20 days later. Hoffmann concluded from the shortness of the incubation period in this case, and from other signs, that *Sp. pallida* circulates in the blood at this stage in a form even more virulent than is found in chancres and papules.

Numerous other points of great interest have also been noted in the course of such experiments; thus, Levaditi and his colleagues, by the use of the pyridine method, have found that the chancre of the chimpanzee contains a much

larger quantity of spirochetes than the chancre of the *macacus*, a fact which coincides with the variation in the character of the disease in the two *genera*. They have also found in the cicatrices of *Macacus cynomolgus* from which the 3 to 5-day-old sore had been excised, that *Sp. pallida* could still be demonstrated, as well as in the gland corresponding to the scar. Neisser's experiments on the infectivity of tertiary lesions have already been mentioned; out of 17 cases in which tertiary products were inoculated into monkeys he obtained 5 positive results, and he is of opinion that every tertiary manifestation should be considered infective.

Rabbits have also been employed, of recent date, for inoculation experiments with the virus of syphilis. In this instance the material is inoculated into the anterior chamber of the eye or introduced into the cornea after scarification. The results have been somewhat contradictory, but in most instances interstitial keratitis develops with or without the appearance of a small tumour on the corneal surface. Siegel, under those conditions, finds in the corneal layers the organism which he has named the *Cytorrhyctes luis*, which, in his opinion, is the cause of syphilis. Others, however, have not been able to confirm Siegel's work, and consider his *Cytorrhyctes* a harmless saprophyte. It has, however, been suggested that it may stand in some developmental relationship to *Spirochaeta pallida*, and it is possible that this may prove to be the case. There is, at least, no question as to the occurrence of *Sp. pallida* in the corneal lesions, as Bertarelli, Greef and Clausen and others have found them in great numbers by the employment of the silver method. Scherber, who repeated the experiments, found no spirochetes, although a keratitis developed, but Bertarelli thinks that his failure was due to the examination of the tissue having been deferred too long, the spirochetes being encountered in the greatest numbers in the early days of the lesion and disap-

pearing later, presumably by migration to the deeper structures.

In a later communication Bertarelli reported that he had been able to transmit the virus from rabbit to rabbit with 100 per cent. of successful results and that, in the process, the virulence of the virus became exalted. The spirochete was always to be found in great numbers and he also thought it possible that secondary symptoms, such as paralysis, may follow inoculation of this "exalted" virus in rabbits. Inoculation of this virus, after passage through several rabbits, produced typical lesions in monkeys, thus demonstrating the specific nature of the lesions in the rabbit. He also succeeded in reproducing the corneal lesions in guinea-pigs, dogs and sheep by inoculation of the rabbit virus of the fifth or sixth passage, the spirochetes being found in the sections of the cornea.

More recently the scrotum and testicle of rabbits have been used for inoculation experiments and have proved more convenient. A piece of syphilitic tissue, chancre or condyloma or a thick emulsion of a culture of *Sp. pallida*, is introduced either into the testicle or under the skin of the scrotum. The resulting lesion, either a nodule in the skin which may ulcerate, or a spreading infiltration, or orchitis, generally commences within six weeks, but when the disease is passed from one rabbit to another by successive inoculations the virus gradually increases in virulence and the incubation eventually becomes as short as two weeks. Recently Sowade claims to have induced constitutional syphilis in rabbits, loss of hair and weight, papular and ulcerating skin lesions, paronychia and iritis by means of intravascular injections of artificially cultivated *Sp. pallida*. Noguchi's experiments with pallida cultures have already been mentioned (p. 33).

Infection.—Animal experiments have done much to in-

crease our knowledge of the pathogenicity of the *Sp. pallida* under different conditions. As might be expected, lesions which contain the spirochetes in greatest numbers are those which are the most successful sources of inoculation and may therefore be considered to be the most dangerous from the point of view of accidental infection. Thus the primary sore, condylomata, mucous patches, and the skin and mucous membrane lesions of congenital syphilis have been shown in this way to be particularly dangerous, though it must be remembered that tertiary lesions, in which it is particularly difficult to find spirochetes, have been successfully used in inoculation experiments.

After removal from the body the *Sp. pallida* quickly loses its virulence and dies. Opinions differ as to the length of time it can remain alive after removal from the body. Levaditi believes that death occurs in 6–8 hours; Beer claims to have kept it alive under anaerobic conditions for 33 days, but this does not seem to be of practical interest from the point of view of accidental infection. In specimens prepared for dark-ground illumination I have occasionally seen independent movement up to two days, but not longer. It is killed at once by drying, with weak antiseptics, and by a temperature of 51°C.

The conditions under which the *Sp. pallida* is most successfully planted on a fresh host are of considerable practical interest. Animal experiments have shown that infection most frequently follows when the virus is planted on or in the true skin. A minute abrasion, not sufficient to draw blood, but enough to cause a slight oozing of serum, is the site on which the parasite can best become accustomed to its new surroundings. Finger and Landsteiner and Pinard succeeded in producing infection under peculiarly difficult conditions, to be mentioned later, by pushing the virus in large amounts into pockets under the epidermis or in the *cutis vera*.

Though these sites are the best for experimental inoculation, it must be remembered that even the lower animals have been successfully inoculated by intravenous injections, injections into the testicle and even subcutaneously, so that it is not absolutely necessary that the spirochete be planted in the skin or mucous membrane for infection to follow. If this is the case with lower animals, which we know are much less susceptible to syphilis than man, it is not surprising that it should occur in man. The undoubted cases in which syphilis has followed an accidental puncture with an infected needle, without the development of a primary sore, are examples of this.

Incubation.—As is well known in the case of man, and has been shown by animal experiments, a period of apparent quiescence follows inoculation before the primary sore begins to appear. In man this period is generally about thirty days. It is not quite clear why such a period should elapse before the tissues react sufficiently to show macroscopic changes. It is certainly not because the spirochete remains entirely inactive during this period, since Levaditi and Yamanouchi have shown that microscopical changes commence very early. These workers believe that the slight reactive changes caused by the presence of the spirochete in the tissues produce increased nourishment for the parasites, which rapidly multiply in the site of inoculation when the nourishing substances have accumulated in sufficient amount.

It might reasonably be supposed that as the incubation period is so long it would be possible to prevent syphilis by excising the site of inoculation at an early date. Unfortunately this is not the case. Neisser found by animal experiments that infection followed the inoculation if excision was delayed for twelve hours. Metchnikoff showed that calomel ointment (30 per cent.) rubbed into the site of an experimental inoculation an hour after it had been carried out pre-

vented infection in the case of a medical student and also of a macaque; but a macaque which was energetically rubbed with the same ointment twenty hours after inoculation developed a chancre. Neisser has infected animals with the blood of monkeys on the fifth day after their inoculation and with the spleen on the twelfth day.

It is evident, therefore, that very soon after inoculation the parasite spreads quickly into the general circulation. It appears to do so chiefly by way of the lymphatics, but there is reason to believe that it also travels, more directly, by the blood vessels.

After the development of the primary sore another period of apparent quiescence follows, and Neisser has shown that during this period, which precedes the so-called secondary stage, the chief sites of the parasite are the bone marrow, spleen and testicle. Before these experiments and the advent of the Wassermann test it was believed that the disease was quite latent between the clinically primary and secondary stages, but the Wassermann test now also shows that although no clinical signs are apparent, the spirochete is by no means inactive, and the same applies to the so-called latent period which succeeds the secondary stage.

It is necessary to emphasize this, since there is too great a tendency to consider that syphilis is latent when clinical signs are absent.

Distribution of the Spirochetes in Syphilitic Lesions.—Our knowledge on this point is almost altogether due to the results of section staining by the silver method, which has not only shown the distribution in the various lesions, but has given much valuable information as to the relationship between the spirochetes and the various tissue elements.

In the primary chancre *Sp. pallida* may usually be demonstrated, either in films or in sections; as will be mentioned, the best method of direct examination is to

scrape the surface of the lesion, allow the discharge to become clear and then to make the preparation. With experience in the technique a large percentage of positive results will be obtained. If the surface discharge, only, is examined the failures will be more numerous; the effect of local treatment must also be borne in mind as there is no doubt that local applications of mercury, etc., bring about the disappearance of both *Sp. pallida* and *Sp. refringens* from the superficial layers of the lesion. By the section method, the relation of the spirochetes to the tissue elements has been closely studied by many observers and it is seen that the spirochetes are mostly to be found in the walls or in the immediate neighbourhood of the smaller vessels and lymphatics, where, at times, they occur in clumps and clusters of considerable size. They have also been found, though not so frequently, in the lumen of the vessels themselves. The sections also confirm the results of film examinations, since they show that the *Sp. pallidae* are most numerous in the deeper parts of the chancre; on the other hand, *Sp. refringens* is confined to the superficial layers. In numbers, the specific spirochetes are often very sparse, especially when the chancre is healing and the induration is diminishing; this is not, however, always the case, as they have been found in great numbers in a chancre which was quite closed and nearly healed, and have even been found in sections of the cicatrix left by an old sore. In the near neighbourhood of the chancre Burnet and Vincent have noted that the spirochetes are most numerous in the epidermal papillae near the ulcer and in the bundles of connective tissue underlying the epidermis.

The indurated glands following on the primary lesion have also been shown to harbour the parasite, both by puncture and by excision and impregnation with silver. In this situation their relation to the smaller blood vessels and lym-

phatics is similar to that noted in respect of the primary sore, viz., they are mostly found lying in the walls of the vessels, in the perivascular spaces and in the connective tissue surrounding these vessels. Much debate has arisen as to the occurrence of phagocytosis; although this does not appear to be common there seems little doubt that it does take place, while the silver-stained granules, noticed in the cells by many observers, may, conceivably, indicate that it takes place on a larger scale than is supposed and passes unnoticed owing to the rapidity of intra-cellular digestion.

In the various secondary eruptions of syphilis the spirochete has often been demonstrated. In sections of a "rose spot," excised when three days old and stained by the silver method, Veillon and Girard found that the capillaries of the papillae and of the sub-papillary zone were dilated, gorged with blood and showed in places around them a commencing infiltration of mononuclear cells; the spirochetes were found in the terminal capillaries of the papillae and in some of the sub-papillary vessels. They regard such spots as being due to a true parasitic embolism.

The occurrence of the spirochetes in the blood is also of the greatest interest, not only as indicating the probable manner in which the disease extends throughout the system, but in view of the known infectivity of the blood in certain stages of syphilis. The occasions on which the parasites have been found in the blood are not numerous, but there appears to be no doubt that they are to be met with here. Leaving out of account, for the present, those instances in which they have been found in the blood of new-born syphilitic infants during life, the following may be instanced. Flügel found them in the blood of a woman at the time she was suffering from a maculo-papular rash. Bandi and Simonelli also detected them in the blood of a secondary case, taken from the neighbourhood of an erythematous lesion of the

skin. In addition, Hoffman has shown, by experiments on monkeys which were inoculated with syphilitic blood, that the disease may be conferred in this way and has, further, noted that the blood in the secondary stage when tested in this manner, appears to be even more virulent than material taken from chancres or papules. Hoffmann's experiments, of course, prove no more than that the blood in question contained the virus of syphilis, but, taken in connexion with the rest of our knowledge of *Sp. pallida*, it is a fair assumption that the blood contained the parasite, though in numbers too small for detection by the methods at our command. This assumption finds further support in the fact that *Sp. pallida* was subsequently detected in the lesions of some of these monkeys, while it has never been found in these animals in any other condition than that of experimental syphilis.

In most of the other lesions of secondary syphilis the parasite has also been found and, as a general rule, it may be said that the more infective the lesion the greater the number of spirochetes that will be detected; in my own experience, the greatest numbers occur in such lesions as mucous tubercles and condylomata. Such lesions are, however, usually ulcerated and one will naturally find in association with *Sp. pallida* numbers of saprophytic or pyogenic bacteria, and probably other spirochetes, such as *Sp. refringens*. This is especially the case in the throat lesions of the secondary stage of syphilis, where the identification of *Sp. pallida* is complicated by the frequent presence of a common throat spirochete, the *Sp. buccalis*. With very little experience, however, little difficulty will be found in distinguishing it from the others.

Among the numerous other sites in which *Sp. pallida* has been found may be mentioned the internal tunic of the aorta; this was noted by Reuter and subsequently confirmed by Schaudinn and is of importance in view of the fact that aortic scleroses have been thought to be late sequelae of syphilis.

Its discovery in the pus of an abscess in a patient suffering from syphilis has also been reported by Flügel.

The relationship, which the *Spirochaeta pallida* bears to the tertiary lesions of syphilis is, at the present moment, uncertain. One of the strongest arguments against the causative rôle of the spirochete was the fact that it is but rarely found in tertiary lesions and, although a certain number of positive cases have been put on record, as will be mentioned below, there is no doubt that their presence cannot be detected in the vast majority of these lesions, even by the silver method of Levaditi. It is possible that the spirochetes may at this time have assumed some other form, such as a resting stage, and in this manner have escaped detection; but it is also possible that these lesions are only late manifestations of the past action of the spirochetes or their toxins, and that when the lesions are recognizable from their clinical symptoms the parasites themselves have disappeared. Assuming the protozoal nature of the parasite, there is reason to anticipate that the latter explanation may be true, on grounds of analogy with other protozoal diseases; for instance, in "sleeping sickness," in the last stages of the disease the trypanosomes cannot be found in the brain, although grave histological changes are always to be met with in the cerebrum and are the cause of the fatal coma in which most cases terminate.

At the same time, a certain number of instances have been recorded in which the spirochete *has* been found in undoubted tertiary lesions; thus, Spitzer found them in sclerosed gummatous lesions and Doutrelepont and Grouven, by the use of the silver method, have detected them in tertiary lesions in four cases. Alvares reported their occurrence in film preparations made after death from the liver of a negro who at the time of his death was the subject of tertiary manifestations, including a typical glossitis and general adenitis.

Tomasczewski investigated a series of tertiary cases and succeeded in proving the presence of *Sp. pallida* in five instances. The cases were all of definite tertiary nature, of 4 to 8 years' duration and were the subjects of gummata, serpiginous syphilides, etc., and the spirochetes were found, not in sections, but in film preparations stained by Giemsa's method. Tomaczewski noted that the spirochetes were extremely rare, and it was sometimes necessary to search the films for 6 to 8 hours to find a single parasite; when found, however, they were unmistakable and presented all the features of Schaudinn's organism.

Some help is again to be had in this question from the results of animal experiments; for instance, Buschke and Fischer succeeded in infecting *Rhesus* monkeys with material derived from malignant ulcerated syphilides and from an ulcerated gumma from a case of syphilis of seventeen years' duration. The spirochete in these experiments was not found prior to the inoculation of the material. Similar experiments were conducted by Neisser, who succeeded in infecting five out of seventeen monkeys by inoculation with material from tertiary lesions.

On the whole, it may be said that the occasional presence of *Sp. pallida* in tertiary syphilis and the results of the animal experiments just quoted are consistent with what is known, on clinical grounds, as to the rare, but occasional, infectivity of tertiary lesions.

The Spirochete in Congenital Syphilis.—Shortly after the announcement of the discovery the spirochetes were found in the bodies of the offspring of syphilitic parents, either still-born or those which had survived their birth for a short time. The introduction of the silver method gave a great impetus to the study of the parasite in these cases and a large volume of literature has already accumulated bearing on this branch of the subject. The purpose of this book precludes

any exhaustive analysis of this work, and it will suffice to indicate the principal points which have been brought out and their bearing upon the questions of the relationship of the parasite to the tissues and the explanation these observations afford as to the manner in which hereditary transmission of the disease takes place.

A striking fact that emerges from a study of this subject is the enormous numbers in which the spirochetes are found and the widespread nature of their distribution in the tissues. There is hardly an organ or tissue in the body of the child in which the spirochetes have not been found and in some instances the numbers disclosed on examination of a section of a congenital liver or spleen are almost incredible.

The following list of the principal sites in which the spirochetes have been found in these congenital cases will give an idea of the manner in which the tissues of a syphilitic foetus may be saturated with the parasite, and will leave little room for wonder that the death of the offspring so often occurs. They have been found in the peripheral blood, the liver, spleen, lung, brain, stomach (in all its layers), mesentery and mesenteric glands, in the gall bladder and bile duct, the thyroid and thymus glands, the walls of the bladder, the kidneys and supra-renals, in periosteum and in bone marrow, in the tonsils and the pharyngeal mucosa. They also occur in the uterus, ovaries, Graafian follicles and in the ovocytes themselves and have been detected in the urine and the meconium. In addition to the above, they have been found in numbers in the skin lesions such as the bullae of pemphigus, and in the peripheral nerves as well as in the optic nerve and retina and the cerebro-spinal fluid.

As regards their relationship to the tissue elements, this appears to be much the same as in the case of acquired syphilis; the spirochetes are chiefly situated extra-cellularly and in the greatest numbers in the walls and in the immediate environ-

ment of the smaller blood vessels and lymphatics; at times they have been seen in the cells of the liver, lung and other organs. The enormous numbers frequently encountered quite bears out the well-established danger of infection from the handling of such diseased material. The finding of the spirochetes in the bile, the urine, the bronchial secretion, the nasal mucus and the meconium sufficiently indicates the infectivity of the discharges from syphilitic infants, while the reality of this danger has been proved by the positive results of the inoculation of such material into susceptible animals such as monkeys. These observations also bear out the well-known risk of infection from a child suffering from hereditary syphilis, as proved by the numerous instances which have been recorded of infection of a healthy wet nurse through the suckling of a syphilitic child.

For further details of the distribution of the parasites in the tissues of congenital cases and of the relationship of the spirochetes to the tissue elements the reader may refer to the work of Buschke and Fischer,[1] of Levaditi and his colleagues,[2] of Bertarelli,[3] Schlimpert,[4] Pasini [5] and others. The exhaustive histological studies of those observers are in close agreement and constitute an exceedingly powerful count in the indictment of the *Spirochaeta pallida.*

Great interest naturally attaches to the distribution of the parasites in the tissues of the parents and the infected offspring from the point of view of determining in what degree this accords with current views as to the mode of transmission

[1] A. Buschke and W. Fischer. *Berlin, klin. Woch.*, p. 6. 1906. *Idem. Berlin. klin. Woch.*, p. 383. 1906. *Idem. Archiv fur Dermatol. und Syph.*, vol. lxxxvii, fasc. 1.

[2] C. Levaditi. *Comptes rend. de la Soc. de Biol.*, vol. lix, p. 342. 1905. *Idem* and Manouélian. *Ibid*, p. 257. *Idem. Annales de l'Institut Pasteur*, vol. xx, p. 41. 1906.

[3] E. Bertarelli. *Central. für Bakt*, vol. xli, p. 639. 1906.

[4] H. Schlimpert. *Deutsche med. Woch.*, p. 1037. 1907.

[5] A. Pasini. *Giorn, italiano d. malatt. vener. e.d. pelle.*, fasc. 5. 1906.

in hereditary syphilis. It is recognized that infection of the child may result from previous infection of either or of both of the parents. In the case of the mother, this may be either by infection of the ovum or by way of the placental circulation, and these alternative methods of infection are quite borne out by the discovery of the spirochete in the placenta, the cord, and in the blood and tissues of the child ; while germ-infection or "ovular" transmission is supported by the finding of *pallida* in the ovaries, Graafian vesicles and even in the ovum itself. The infectivity of these tissues has, further, been abundantly proved by the results of animal experiments. With regard to paternal transmission, the subject of much controversy in the past, we now have positive knowledge, long in default, that the semen of a syphilitic father contains the virus of the disease, as shown both by the inoculation of testicular matter from infected monkeys into other monkeys, and, also, from the inoculation into monkeys of human semen from a man in the secondary stage of the disease. The argument that the head of a spermatozoon is too small to allow of the penetration of the *Spirochaeta pallida* is not valid, as there is no reason why the spirochetes should not be conveyed to the ovum together with the spermatozoa, and infect the germ cell at a subsequent stage of its development.

As regards "conceptional syphilis," i.e., infection of the mother from a foetus syphilized by spermatic infection from the father, an occurrence long suspected but difficult of proof, an interesting case has been put on record by Buschke and Fischer. In this, the mother, apparently healthy, but married to a syphilitic man, gave birth to a syphilitic child and subsequently manifested the disease, the spirochetes being found on aspiration of an indurated gland in her groin. Delayed conceptional syphilis, in which the mother is infected from the child and develops tertiary symptoms some years later, is explicable in view of the long periods for which the

spirochete may remain latent in the tissues, as evidenced by its discovery in tertiary lesions many years after the date of original infection. Possibly, then, the spirochete may not only pass through the placental circulation from the mother to the foetus, but may travel in the opposite direction and carry infection from a syphilitic child, infected by the sperm of the father, to a previously healthy mother. Since the case of Buschke and Fischer was recorded, however, it has been found that a very high percentage of apparently healthy mothers of syphilitic infants give a positive Wassermann reaction, so that there is no proof that in this case the mother was not infected before conception.

There is, as yet, no evidence to be derived from the spirochete in support of the transmission of syphilis to the third generation, but there is strong presumptive evidence in the knowledge that the parasites may enter the Graafian vesicles and infect the ovum; it by no means follows that such infected ova are incapable of further development and of ultimate fecundation; such a child might survive and live to give birth to syphilitic offspring.

In general, then, it would appear that the distribution of the spirochetes in the tissues of the parents and the offspring is quite in accord with our knowledge of the mode of transmission in congenital syphilis, and, indeed, forms a tribute to the accuracy of much of this knowledge. It is true that the evidence rests chiefly on the results of the examination of the tissues by the silver method, and that some doubts have been cast upon the validity of this evidence but these doubts are entertained by a very small minority of observers and will probably vanish as experience accumulates. It must be further borne in mind that the evidence, does not rest solely upon the "silver spirochetes" as, in a certain number of instances, in which the child has lived for some days or weeks, the spirochete has been demonstrated during life in

the peripheral blood, in films stained by Giemsa's method. This proved existence of a "spirochete septicaemia" in cases of congenital syphilis constitutes a piece of evidence the value of which it is hard to minimize.

Immunity.—It cannot be said that immunity, natural or artificial, in the sense with which this term is applied to such diseases as smallpox, typhoid fever and so on, has ever been proved in syphilis. The existence of a natural immunity is, under the circumstances, impossible of proof. With regard to immunity acquired on recovery from syphilis, this is so little the case that the occurrence of a second attack of syphilis is held to be strong evidence that the first attack was cured. No great success has followed attempts to produce an artificial immunity by inoculation with virus which has been killed, or attenuated for man by passage through monkeys or by previous mixture with chemical agents. The great objection to any attempt to produce protection with attenuated virus is the fact that it is impossible to prove absolutely that a person who has been infected is cured, and after being quiescent for many years syphilis may break out again in a much more serious form. Infants suffering from congenital syphilis are improved by imbibing the milk of their mothers who have been treated with salvarsan, and Ehrlich believes that the therapeutic effect is due to immune substances in the milk, since this has been found to contain only minute traces of arsenic ; so little, in fact, that the amount contained in a week's supply corresponds to much less than a therapeutic dose of salvarsan. We do not yet know, however, in what form salvarsan destroys *Sp. pallida.* It cannot be in the form in which it is injected, since salvarsan has very little action on spirochetes *in vitro*, and it seems quite possible that the spirocheticidal product of salvarsan which is produced by the mother's tissues may contain arsenic in very minute amounts and may be secreted in the milk.

The only evidence of immune substances existing in syphilitic blood is provided by the experiments of Noguchi and of Craig and Nicholls on complement deviation by the serum of syphilitic persons in combination with extract of cultivated *Sp. pallida*, and even here it is not certain that spirochete extract does not work in the same manner as extract of normal organs, by virtue of its content in lipoids (see p. 84).

Though immunity in the true sense of the word has not been proved, from an early date in the infection the skin and mucous membranes of syphilitic persons are increasingly resistant to fresh infection, till after the fifteenth day following the appearance of the primary sore it is practically impossible to produce a second chancre. As the first chancre becomes older the incubation period of the second becomes shorter and shorter, and the resulting sore more and more unlike a typical chancre. In the secondary and tertiary stages of syphilis Finger and Landsteiner succeeded in producing skin lesions, but only by introducing very large amounts of syphilitic material into pockets in the true skin. The resulting lesions were not true chancres, but corresponded in character to the lesions which would be expected in the stage of syphilis at which the inoculated patients had arrived. Thus in the secondary stage papules followed the inoculation, and ulcerating syphilides in the tertiary.

Consequent on the well-known refractory response of syphilitic tissues to fresh syphilitic infection, the syphilitic origin of parasyphilis has received strong support from the experiments of Krafft-Ebing, who failed to produce primary sores by inoculating with syphilitic material nine cases of tubes.

The evidence at present, therefore, shows that so long as the spirochetes are active in the tissues of the patient (at any rate from a very early date) the tissues are almost absolutely resistant to fresh infection, while the experiments of Finger

and Landsteiner, already mentioned, indicate that when the tissues are re-infected with virus introduced from without the character of their response depends on the age of the first infection and probably therefore on the length of time during which *Sp. pallida* has been acting on them. The last remark applies also to the tissue response to any renewed attacks by spirochetes already resident in the patient, and can be ascribed only to intimate changes in the tissues resulting from the continued action of the spirochetes. In a communication to the *Journal* of the Royal Army Medical Corps in 1911, the writer drew attention to the fact that in patients who relapse even many months after treatment with salvarsan, and when the Wassermann reaction has been negative till shortly before the clinical relapse, or is negative at the time, the character of the relapse is very often a reproduction of the symptoms for which the patient was first treated. Thus if treatment commenced in the primary stage the relapse is very often a chancre, and if in the early secondary stage, early secondary symptoms reappear. This appears to the writer to show that in these cases salvarsan has brought the spirochete's activity to a complete standstill; has produced, in fact, a true latency, which contrasts with the apparent latency produced by mercury, since under this remedy the relapse generally assumes a later character, indicating that since the date of the last outward manifestations of syphilis the spirochete has been constantly acting on the patient's tissues.

Histology.—Every manifestation of syphilis when examined microscopically is seen to consist of a cell infiltration, principally in and around the smaller blood vessels. For practical purposes the exact nature of the infiltration matters little, but the fact that it possesses a marked tendency to form fibrous tissue is of great importance, as this explains the induration of so many syphilitic lesions. The degree of induration

depends on the normal structure of the part and the extent to which the fibrous change has progressed. Thus the Hunterian chancre feels like a piece of cartilage, the syphilitic lymphatic gland like a solid rubber ball, while the roseolar syphilide imparts no sensation of induration and the infiltration has to be looked for with a microscope. Excessive proliferation of epithelium sometimes take place as in the mucous tubercle or scaly papule. A useful fact to remember when examining a squamous eruption is that every scaly syphilide is distinctly indurated, a condition which at once distinguishes it from psoriasis. In the so-called primary and secondary stages of the disease this infiltration has a tendency to undergo involution and become absorbed, while in the tertiary lesions caseation and breaking down are the more probable terminations.

CHAPTER III

DEMONSTRATION OF THE SPIROCHAETA PALLIDA AND ITS DIFFERENTIATION FROM OTHER SPIROCHETES

The *Spirochaeta pallida* can be demonstrated in serum expressed or aspirated from syphilitic lesions or in sections of infected tissues after removal of the latter from the body.

In serum from syphilitic lesions it may be examined fresh by means of the dark-ground illumination, or in films. In the latter case the exudate is mixed with some preparation such as Chinese ink, which will stain the background without touching the spirochetes, or the film is stained so as to dye the parasite.

Of all methods examination by dark-ground illumination is undoubtedly the most convenient, rapid and certain. This is so much the case that since the perfection of this method the *Sp. pallida* from being one of the most difficult organisms to demonstrate has become one of the very easiest.

The value of a routine microscopic examination of the serum from any suspected early syphilitic lesion cannot be too strongly emphasized. It affords a practicable means of diagnosing syphilis long before the clinical signs are clear or the Wassermann reaction has become positive, and in secondary lesions a diagnosis can frequently be made by a microscopic examination without recourse to the Wassermann test, which even in this stage may occasionally be negative, and in any case entails delay and a more complicated procedure. In illustration I may mention that I have demonstrated *pallida*

in chancres no larger than a pin's head, in a chancre on the inferior turbinate bone, in secondary skin lesions when the Wassermann reaction was negative and in all varieties of secondary mouth and throat affections.

In pre-salvarsan days the early diagnosis and treatment of syphilis were considered of great importance. They are infinitely more so now that salvarsan has been introduced, since the experience of all who have used this remedy shows that the great opportunity of curing the disease rapidly is in the very early stage before the sore has become indurated, the glands enlarged or the Wassermann reaction positive; in fact, in the stage when nobody would venture to diagnose syphilis on clinical grounds.

The surgeon who would give his primary case the best chance should think first, therefore, not of induration, nor of glands, nor even of a blood-test, but of microscopic examination of the exudate from the sore for *Sp. pallida*, and should lose no time in carrying this out or having the examination made for him.

Whichever method of demonstrating the spirochete is chosen the manner of collecting the serum exudate is the same and may be considered first.

The general principles are to obtain serum from below the surface and to avoid as far as possible contamination with surface, organisms and too great admixture with blood cells. Surface organisms often include other spirochetes, which may be very fine and tightly rolled and are apt to confuse the beginner. Blood cells obscure film preparations and in fresh specimens may reflect too much light into the field.

The lesion (chancre, condyloma, papule, mucous patch, etc.) should first be cleaned, by rubbing it over with wool or gauze soaked in saline, and then dried. In dealing with a chancre which is within a tight prepuce it may be difficult to keep the surface of the sore clean on account of pus welling out from

behind the prepuce. In such cases it is well to pack in some dry cotton wool behind the sore so as to isolate it. The specimen should be obtained from the margin of the lesion, especially if it is ulcerated. This may be lightly scratched with the edge of a scarifier so as to remove the superficial epithelium without, if possible, drawing blood; or rubbed over with spirit, which is then dried off; or the point of a capillary pipette may be run in below the surface and the serum drawn out by means of a rubber teat. Of these I usually employ the scarifier.

In some situations, e.g., on the fauces or within the nose, it may not be possible to reach the sore by any of these means and I have found the following plan very successful. A capillary pipette is cut off square to a convenient length; the open capillary mouth of the pipette is then rubbed lightly over the surface of the lesion and as this becomes abraded the blood and serum which exudes flows along the pipette; a very small drop is all that is required. Sometimes, as in the case of a secondary rash, it may be difficult to induce serum to exude. Here, if practicable, a blister may be applied and the blister fluid examined, but generally it is only necessary to apply some form of suction after scarifying the surface. The simplest way of doing this is to smear the mouth of an ordinary test-tube with vaseline, heat the blind end of the tube in a flame, and then apply the test-tube so that its mouth encircles the scarified area; the test-tube acts, of course, just like a cupping glass. If from any of these procedures blood flows too freely it should be gently soaked up with a little wool or gauze, and the operator should wait for a few minutes till the blood clots. The best specimens are made with clear serum, and at most the serum should be light pink.

To obtain serum from a gland, having sterilized the overlying skin, the gland is picked up with a finger and thumb,

and the needle of an all-glass hypodermic syringe run into its substance. The needle-point is worked about a little within the gland and suction then applied with the piston of the syringe. The needle is withdrawn, and the aspirated material, which may fill only the needle, forced out into a watch-glass, where it can be emulsified with a little saline or distilled water according to the method of examination to be employed.

The further procedure will be described under each of the methods of microscopic examination, but it may be mentioned here that if the operator wishes to send the specimen to a laboratory for examination, it is by far the best plan to allow the serum to run into a capillary tube, shake the column of fluid down till it is about an inch from the capillary mouth, and then seal off with a fine flame above and below the specimen. This gives the pathologist full choice of methods of examination.

Dark-Ground Illumination.—This method of examination was invented many years ago, but until quite recently was only suitable for low-power objectives, and was not greatly employed in bacteriological technique. The difficulty of seeing the *Sp. pallida* under axial illumination, such as is used for ordinary hanging drop specimens, led to the introduction of the present perfected apparatus into the bacteriological laboratory.

A microscope which is fitted for dark-ground illumination is sometimes called an ultra-microscope, a term which seems unfortunate since it is inappropriate and also conveys the idea that a dark-ground apparatus means a microscope which is specially built for the purpose, and not, as it does, simply an ordinary bacteriological microscope with one or two accessories for use when required.

Of these accessories the chief is a special condenser which is fitted in place of the ordinary sub-stage condenser. The

object of this condenser is to direct the rays of light from the mirror of the microscope so that they strike solid objects in the specimen at a very oblique angle, as is illustrated in the accompanying photograph (Fig. 1), which shows the path of rays from a Leitz concentric condenser. In this it will be seen that the rays come to a very sharp focus and diverge again at a wide angle. If, in place of the condenser usually supplied, the microscope is fitted with a spherically and chromatically corrected oil-immersion condenser of N.A. 1·4, efficient dark-ground illumination can be obtained by placing a central stop on the diaphragm carrier. Such an arrangement

Fig. 1.

costs no less than the usual one of having the ordinary type of condenser for stained specimens and another, special, condenser for dark-ground work, but it has the advantage that for ordinary work a better condenser is used and for dark-ground the change in the sub-stage illumination can be made instantly.

The mechanism of the two main forms of special dark-ground condenser will be understood from a study of Figs. 2 and 3, and it is only necessary here to describe generally the path of rays after leaving the condenser in order that the directions for using it may be understood.

Leaving the upper surface of the condenser the rays pass unrefracted to their focus on the upper surface of the micro-

scope slide. For this two conditions are essential: (1) a film of cedar-wood oil or distilled water must be interposed between the slide and the condenser, and (2) the slide must be of the thickness, or at any rate no thicker than that, which is suitable for the particular make of condenser in use; otherwise the focus would fall within the substance of the slide. Reaching the upper surface of the slide, where they are focussed, those rays which meet no solid object pass on to the coverslip, and their further course is determined by the medium which is above the coverslip. If this is air, as when a dry objective is being used, they are reflected from the upper surface of the coverslip and lost; if the medium above the coverslip is oil, as when an oil-immersion objective is employed, the rays pass on but are not taken up by the objective provided that the numerical aperture of this is less than 1. In either case the result

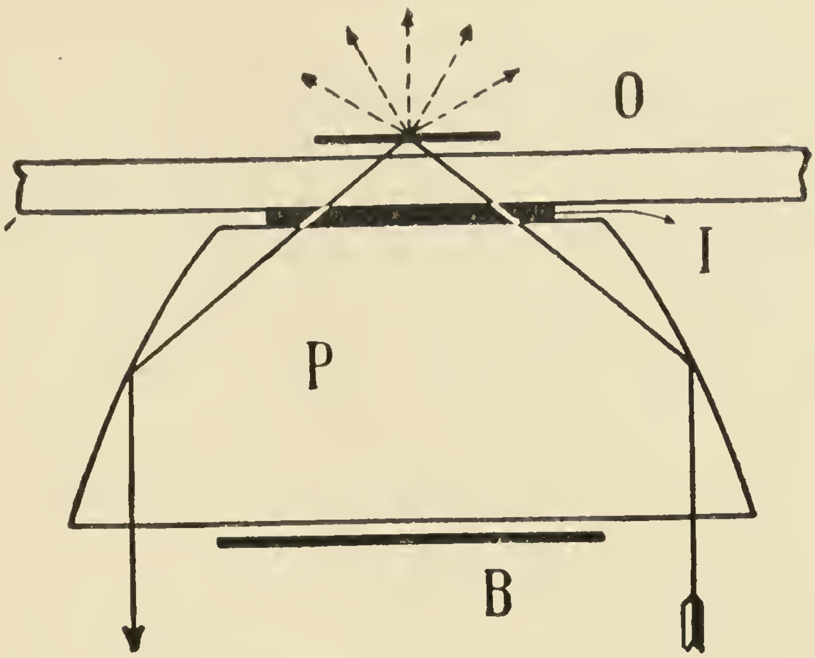

Fig. 2.—Mechanism of Zeiss Dark-ground Condenser.

P: Plano-convex body of glass, the convex surface being formed by a paraboloid of rotation.
B: Central stop to cut off central rays from mirror.
I: Immersion fluid between condenser and microscope slide.

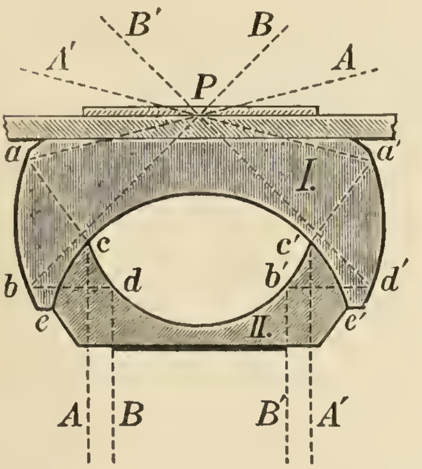

Fig. 3.—To illustrate Path of Rays in Leitz Dark-ground Condenser.

Lower *A B B*¹ *A*¹: Rays from the mirror.
*c d b*¹ *c*¹ Points where rays from the mirror are first reflected.
*a b a*¹ *d*¹ Points where rays are next reflected.
P Focus of rays on upper surface of slide.
Upper *A*¹ *B*¹ *B A*: Final course of rays when medium above cover-slip is homogeneous with glass (cedar-wood oil).

is darkness and this constitutes the dark background. As the numerical aperture of all oil-immersion lenses is more than 1, when such an objective is used it is necessary to stop it down. This is done by means of an inexpensive device, which is the second accessory required to convert an ordinary microscope to a dark-ground apparatus. Those rays of light which meet solid objects (spirochetes, blood cells, bacteria, etc.) in the specimen are deflected upwards by these and, entering the microscope, are seen in the image which is viewed with the eyepiece. Thus the picture of bright objects on a dark background is produced.

There is only one further point to mention before passing on to the technique of mounting the specimen for examination. If the rays of light passing through the film of oil or water which is interposed between the slide and condenser meet an air bubble, however minute, they are deflected upwards and, passing almost vertically through the specimen, illuminate the whole field, destroying the background. Consequently it is necessary to avoid the inclusion of bubbles in this film.

The following directions will be found applicable to the mounting and examination of most specimens. (1) Transfer the drop of serum to a thin coverslip by touching it with the latter held in a pair of Cornet forceps, or by forcing the serum from a capillary tube on to the coverslip. The latter operation is most safely done by breaking one end of the capillary tube and holding the other in a flame; the expanding hot air drives the serum before it out of the tube. If the drop is too minute to fill the space between slide and coverslip, or if it contains much blood, a drop of 0·5 per cent. salt solution should be added.

(2) Turn the coverslip over and drop it gently on a slide of the correct thickness (as recommended by the maker of the dark-ground condenser in use), so as to form a film which

is as free from air bubbles as possible between the slide and coverslip.

(3) Make the film as thin as possible (so as to bring the solid objects in the specimen close to the surface of the slide) in the following way. Fold a piece of lint or filter paper into a number of thicknesses and spread it out on the thigh ; then turn the slide over and press it very firmly, with the coverslip down, on the absorbent surface.

(4) Ring the coverslip with vaseline.

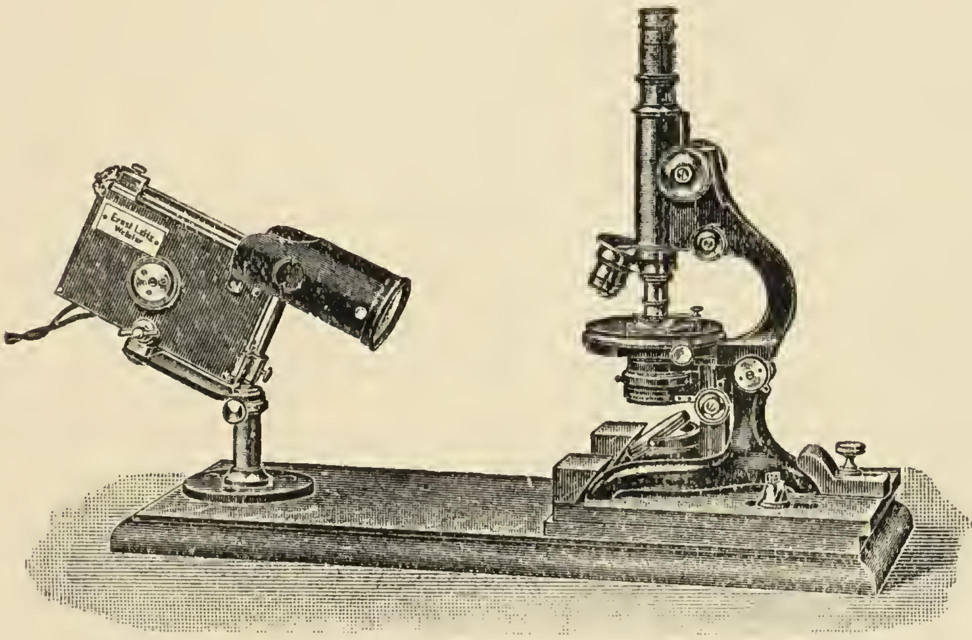

Fig. 4.—To illustrate a convenient arrangement of Microscope and Lamp for Dark-ground Illumination.

The lamp is a Lilliput arc, with bull's-eye set at correct distance in the sleeve.

(5) Arrange the light with relation to the microscope so as to get the best possible illumination of the mirror. The source of illumination may be chosen from a number of sources, of which the following may be mentioned : sunlight ; electric, arc or Nernst ; incandescent mantle, coal gas, spirit vapour, or petrol vapour ; and paraffin oil. Generally speaking, especially when using the Leitz pattern of condenser, which requires a less intense source of illumination, it is not necessary to employ a bull's-eye condenser when using arc or Nernst lamps, and the Leitz pattern condenser gives an

excellent image without a bull's-eye with an ordinary inverted gas mantle when the concave mirror is used. Assuming that a bull's-eye condenser is being used, arrange this about ten inches from the plane mirror of the microscope and place the light behind it so as to throw an image of the illuminant on the plane mirror. This can be judged by holding a piece of white paper over the mirror. The light should fill the mirror as completely as possible.

It may be necessary to centre the dark-ground condenser. The Zeiss condenser should be central when slipped into its sleeve, but other patterns, notably the Leitz, need centring. To do this, rack up the condenser till it is flush with the microscope stage and view its upper surface through a low-power objective (two-thirds) and a low eyepiece (No. 2), bringing the two concentric rings engraved on its upper surface into focus. If the rings cannot be seen the top of the condenser should be cleaned with xylol. By means of the centring screws bring the rings into the centre of the field.

(6) Place a drop of distilled water, or cedar-wood oil, on the top of the condenser and another on the under surface of the slide opposite the coverslip. Turn the slide over and, having racked down the condenser slightly, place the slide on the microscope stage, coverslip up, so that the drop overhangs the condenser. Rack up the latter till it is flush with the stage. The two drops coalesce and here, as already mentioned, it is necessary to see that no air bubble has been imprisoned between the slide and condenser.

(7) If the light has been correctly arranged, with a little manipulation of the mirror a light area should be apparent in the middle of the coverslip. It is useless attempting to view the specimen till this area has been obtained.

(8) Adjust the condenser finally so as to obtain the best possible focus. To do this, view the specimen with the low power objective, etc., used for centring, and a bright area

will be seen in the centre of the field when the preparation is in focus. With the objects in the specimen in focus, rack the condenser slightly up or down so as to reduce this spot to its smallest dimensions. If the bright area is not in the centre of the field manipulate the mirror so as to bring it central.

(9) The specimen may now be viewed with a higher power objective ($\frac{1}{12}$ in. oil-immersion, with No. 4 or 8 eyepiece, 4 mm. apochromatic, or $\frac{1}{6}$ in. with a No. 8 or 18 eyepiece). Generally speaking, the higher the eyepiece the more powerful should be the source of illumination. With a $\frac{1}{6}$ in. or a 4 mm. apochromatic objective and a No. 8 eyepiece the specimen can rapidly be viewed, and it is not necessary to employ high magnifications for diagnostic work.

Film Preparations—Burri's Method.—The principle of this is that Chinese ink will become incorporated with the medium in which spirochetes, blood cells, etc., are suspended, but will not penetrate these. Consequently, when a drop of syphilitic exudate is mixed with a drop of Chinese ink and the mixure spread like a blood film the background is stained black but spirochetes appear as white spirals. Briefly, it is another method of obtaining a dark background. The best ink for the purpose is Günther-Wagner's waterproof Chinese ink, and to make it homogeneous it should be well centrifugalized before use, or, as Captain A. T. Frost recommends, mixed with tincture of iodine in the proportion of one of iodine to 600 of ink. A drop of the prepared ink and one of the suspected exudate are mixed together at one end of a microscope slide and with the end of another slide a thin film is spread. When dry the film is examined with an oil immersion lens. The spirochetes appear as white spirals on a granular black background. Opinions differ as to the reliability of this method of demonstrating the *Spirochaeta pallida*. While some maintain that it is absolutely reliable for diagnostic purposes, others hold that by this method other spirochetes

may be made to appear like *Sp. pallida.* McIntosh and Fildes object that in a thinly spread film *Sp. pallida* may appear abnormally thick and in a thick film other spirochetes may appear abnormally fine; that great distortion occurs and that the most important differential sign, that of motility, is lost. In the writer's experience the greatest objection is the loss of motility, with the knowledge that very fine spirochetes are often seen in living specimens which are chiefly distinguished from *Sp. pallida* by the character of their movements. At the same time one must admit that so far in examining specimens containing only these very fine spirochetes, but not *Sp. pallida*, both by dark-ground illumination and by the Burri method, it has been easy to exclude *Sp. pallida* in the Burri specimen on account of the fact that when spread in films the other spirochetes have lost much of their corkscrew formation. The writer, however, prefers the dark-ground illumination method of diagnosing *Sp. pallida*, as being free from any objection and more rapid.

As a substitute for Chinese ink, and one which at once gives a more homogeneous field than ink, I have found that a suspension of collargol has many advantages. The suspension is made up according to the directions of the makers (Chemische Fabrik von Heyden), one part of the powder being placed in a black bottle (or an ordinary bottle covered with black paper) and nineteen parts of distilled water poured on it. After standing for a few minutes the bottle is well shaken and again allowed to stand. A few minutes later the bottle is again shaken and the suspension is then ready for use. It is used exactly in the same way as Chinese ink, and on examination the spirochetes appear as white spirals on a reddish brown background which is almost perfectly homogeneous. This modification requires a light which is rather stronger than that which is necessary for the Chinese ink specimen, but good daylight is quite sufficient.

Staining.—As has been said, the failure to detect the spirochete at an earlier date was due to the fact that special staining methods were necessary, and such have only been available during the last few years. While this is true, our extended experience shows us that its demonstration in film preparations is not such a difficult matter as was at first imagined, and there are now a considerable number of alternatives to the method by which it was first demonstrated by Schaudinn and Hoffmann, viz., Giemsa's modification of Romanowsky's stain. On the whole, it is an organism which exhibits an extremely feeble affinity for the ordinary basic dyes employed in bacteriology, and, although it may be coloured by the most powerful of those, the results are poor, owing to the deposit which usually occurs on the film and masks the delicate little threads.

The best results are certainly attained by some of the many modifications of Romanowsky's chromatin-staining method, although, for certain purposes, such as the demonstration of the terminal flagella, good results are claimed for the employment of some of the ordinary flagellar stains, for instance that of Loeffler.

Staining of Film Preparations.—It is necessary to observe certain precautions in preparing the film if the best, or indeed if any, results are to be expected. The slide or cover-glass, on which the film is to be made, must be perfectly clean and free from grease ; any of the methods recommended for the preparation of slides for flagellar staining will answer the purpose, but perhaps the simplest is to pass the slide thirty or forty times through the flame of a bunsen burner. Next in importance, the film must be as thin as it is possible to make it. The material may be lightly rubbed over the surface of the slide, or, if of fluid consistency, it may be spread by any of the means employed in the preparation of blood films. If, in either instance, the film is too thick, failure is

sure to result, since the spirochetes will only take the stain when lying in a thin layer of the surrounding medium ; again, if the material is thickly spread, the formation of deposit is favoured, and, if this occurs, there is little hope of being able to recognize them.

Giemsa's stain, which was the one with which the spirochete was originally detected, is still that which is most frequently employed for its detection, and an account may now be given of the manner in which it is used. The staining fluid itself demands a considerable amount of trouble in the preparation, but may now be purchased from the usual dealers in microscopical necessaries made up and ready for use.

The films are allowed to dry in the air and are then fixed, for 15 to 20 minutes, in absolute alcohol. (Hoffmann and Halle recommend, instead, fixation by means of the vapour of a mixture of osmic and glacial acetic acids.) The alcohol is then removed by blotting the film with filter paper. The staining fluid described above is now diluted in a graduated glass, in the proportion of one drop of stain to one cubic centimetre of water. The diluted stain is poured on to the film and allowed to act for one hour ; at the end of this time it is washed off the film by means of a strong stream of water ; the film is then blotted with filter paper, dried in the air and mounted in Canada balsam. In his latest description Giemsa adds that, for the purpose of staining spirochetes, it is well to add to the water, before it is mixed with the stain, 1 to 10 drops of a 1 in 1,000 solution of sodium carbonate. Overstained specimens may be differentiated by soaking them in distilled water for 1 to 5 minutes.

The above method certainly gives very clear and sharply stained results, but the time occupied is long and, occasionally, with the greatest precautions, a considerable amount of deposit forms on the film ; this it is extremely hard to get rid of, as the attempts to dissolve it off by alcohol and other expedients

usually result in the spirochetes being decolourized. Leishman's stain appears to present some advantages over Giemsa's in the above respects and, as it will probably be more accessible to the readers of this chapter, an account may be given of the manner in which it is employed for the demonstration of the spirochetes. For this purpose it may be used in three alternative ways. The details are as follows :—

1. The procedure described for ordinary blood-staining may be used, if the time is increased from 5 minutes to 30 minutes. In this method the fixation of the film is carried out by the action of the stain, and double the quantity of distilled water is added to the stain after 30 seconds, the two fluids being well mixed with the help of a needle passed backwards and forwards through the stain. The stain is then washed off in a little distilled water, the film blotted with cigarette paper, dried in the air and mounted in balsam.

2. In this, the "serum method," which is employed for the production of chromatin staining in sections, is applied to the staining of films. The film, prepared with the precautions advocated above, is fixed with methyl alcohol for half a minute, this is blotted off with cigarette paper (which will be found much better than filter paper) and a thin layer of fresh blood serum is run over the surface of the film. The serum may be obtained from blood drawn from one's own finger in the same way in which a sample of blood is collected for the agglutination test. One drop only is required and is drawn over the film with the help of a needle. The excess is then removed by allowing the slide to remain on its end for a few minutes, when the drop which has drained to the end of the slide is wiped off. The film is then allowed to dry in the air. When dry, the staining fluid is prepared by mixing, in a clean watch-glass, an equal number of drops of Leishman's stain and distilled water. The mixture of stain

and water is now poured on the prepared film and allowed to act for 25 minutes, at the end of which time it is washed off in a gentle stream of distilled water, the film blotted as before, dried and examined, either directly in a drop of cedar oil or after being mounted in balsam. The action of the blood serum is twofold, it intensifies the action of the stain and it obviates the dangers of the preparation being spoilt by the occurrence of deposit. The staining, in a successful preparation, should be carried to such a degree that the nuclei of any cells that may be present should appear almost black. (*See* Plate I.) If this is the case there will be little difficulty in detecting the spirochetes, which will be seen to be sharply stained and easily recognizable with an ordinary twelfth-inch immersion lens.

3. As a third alternative, good results follow when the stain is employed without previous fixation of the film. The method is similar to that which Leishman advocated some time ago for the staining of malarial parasites. In this case the stain and water, in the usual proportion of two parts of water to one of stain (which will be found to be contained in about the same number of drops), are mixed beforehand in a watch-glass and poured directly on to the unfixed film. Optimum staining takes place in about the same time as in method number 2, viz. 25 minutes, and the only additional precautions to be observed are that the distilled water used for washing off the stain must be employed with great gentleness and that the blotting with cigarette paper must be done by slight pressure and without any rubbing. By this procedure the red cells are, of course, de-haemoglobinized and, in addition, a great deal of detritus is dissolved off from the film ; the leucocytes and tissue cells remain and also bacteria as well as the spirochetes, should any be present in the film. This method has the advantage that the greater freedom of the film from débris and extraneous matter makes the

detection of the spirochetes easier. If the precautions mentioned above are observed, there does not appear to be any diminution in the number of the spirochetes, when compared with a fixed film from the same case. On the contrary owing to the deeper staining of the spirochetes, they frequently appear to be more numerous than in the fixed films.

Of the three methods described the last appears to be the best because of the clearer character of the film and because the spirochetes are much more darkly stained, so that, if they are only present in very small numbers, they are less likely to be missed. In searching the film one must remember that the thinner zones are those in which the spirochetes are most darkly stained and therefore most easy of detection.

Most of the other modifications of Romanowsky's method will demonstrate the parasites satisfactorily, that of Marino having been specially advocated by Metschnikoff and Roux.

Of other staining methods, such as that of Reitmann (phosphotungstic acid and carbol fuchsin), of Herxheimer and Huber (Nile blue and Capri blue), of Proca and Vasilescu (Rossi's flagella stain followed by carbol-gentian-violet), and numerous others, it may be said that, while they doubtless stain the parasites with sufficient clearness, most are subject to the disadvantage of excessive deposit on the film, and they do not appear to present any great advantages over one or other of the modifications of Romanowsky's method. As said before, the staining of the spirochetes is by no means as difficult an operation as was at first supposed, and, as long as the film is prepared as directed above and a sufficiently powerful stain is employed, they may be detected with comparative ease.

To a different category belong the flagellar stains used to demonstrate the flagella of bacteria; many of these have been advocated for the purpose of colouring the terminal flagellum of the *Sp. pallida*, described by Schaudinn. Some

of these stains give very clear results and are useful for ordinary diagnostic work; Loeffler's and de Rossi's appear to give the best preparations, though the spirochetes are never so sharply defined as by the methods advocated above.

In general, the beginner may be advised to make trial of several alternative methods on films prepared from the same material and rich in spirochetes, and to adhere to that which gives him the best results as regards simplicity of technique, sharp definition of the parasites, and economy of time.

It is necessary, in view of the minute size of the organism, to employ a good oil-immersion lens, but nothing higher than a 1/12 in. is necessary for the purpose. Good illumination is, of course, essential, and careful focussing of the sub-stage condenser greatly helps the search. Another important desideratum is patience; at times the spirochetes may be rapidly found but, in the greater number of instances, a careful search, prolonged possibly over several hours, is necessary and, unless this amount of time is devoted to the search, one would not be justified in concluding that the parasites were absent. The time occupied by so long a search constitutes one of the greatest objections to this procedure as a means of diagnosis, but the observer will find that, with practice, he will be able to shorten the period considerably and it is a matter of common experience that, with increasing facility of technique, the spirochetes are found in a larger proportion of cases and in greater numbers than in one's earlier attempts.

Staining of Sections.—The demonstration of the spirochetes in the tissues by the method now to be described, has been of great service in adding to our knowledge of their distribution in the various lesions of syphilis and in strengthening the chain of evidence as to their causative rôle. The ordinary staining methods were of no service for this purpose, and it is hardly too much to say that the discovery of

the method by which the spirochetes are coloured *in situ* is second only in importance to the discovery of the parasite itself. By means of it a large amount of the most valuable information has been recorded which has thrown a flood of light on the connexion of the parasite with the disease.

The method, which is usually associated with the name of Levaditi, had its origin in the work of Bertarelli, Volpino and Bovero, who succeeded in staining the spirochete in sections by means of a modification of Van Ermengem's flagella stain. This well-known method presents, however, the disadvantage that it is almost always accompanied by a considerable precipitate of metallic silver on the film, and, when it is attempted to apply it to sections instead of to thin bacterial films, this precipitate is still heavier and tends to mask such delicate structures as the spirochetes. Levaditi then introduced a great improvement by staining the tissues *en bloc*, in place of applying the stain to the section itself, and, in this manner, succeeded in getting excellent results. In the first method described below, he adapted Ramon-y-Cajal's method of staining nerve fibrils in sections by impregnation of the tissue with nitrate of silver and subsequent reduction of the silver by pyrogallic acid. The spirochetes were then seen to be intensely stained by the silver and perfectly black, standing out from the other tissue elements with startling distinctness. The excellent coloured plates which accompanied Levaditi's article by no means exaggerate the picture which is presented by a tissue rich in spirochetes. (Plate I.)

Subsequently Levaditi published a further modification of this method, which, although somewhat more complicated, gives, in his opinion, still better results, inasmuch as it shows more of the spirochetes, when tested on the same tissue, than are put in evidence by his first method. This being so, it follows that, in material containing few spirochetes, success

is more likely to result from the employment of his later method.

The details of both of these methods are given below in order that any who wish may be able to compare the results and select that which suits them best.

Method 1.—Small pieces of the tissue are excised and treated in the following manner :—

1. Fix in 10 per cent. solution of formalin for 24 hours.
2. Harden in 95 per cent. alcohol.
3. Wash in distilled water for several minutes.
4. Place the pieces in a solution of nitrate of silver, of the strength of 1·5 per cent., prepared with distilled water, and leave them in this solution for three days at a temperature of 38°C. (The best way of doing this is to place the bottle in the hot incubator.)
5. The silver is now reduced by placing the tissue for twenty-four hours in the following solution—

Pyrogallic Acid	4 grms.
Formalin.	5 c.cm.
Distilled water.	91 c.cm.

6. Wash in distilled water, dehydrate in absolute alcohol and clear in xylol.
7. The piece is finally imbedded in paraffin and sectioned in the usual manner.

The sections, which should be as thin as possible, may either be examined directly after mounting in Canada balsam, or, if preferred, they may be counterstained by Giemsa's solution, employed undiluted and allowed to act for three to four minutes. Levaditi recommends that, if this is done, the section should be differentiated by means of a mixture of alcohol and oil of cloves.

Method 2.—In this, Levaditi takes advantage of the action of pyridine to hasten the impregnation of the tissue with the nitrate of silver. The use of this substance was intro-

duced into histology by de Souza, who found that it had the power of penetrating tissues soaking in water with exceptional rapidity. The details are as follows :—

1. Fix small pieces of tissue, 1 to 2 mm. in thickness, for 24 to 48 hours, in a 10 per cent. solution of formalin.
2. Harden in 96 per cent. alcohol, for 12 to 16 hours.
3. Wash in distilled water until the pieces sink to the bottom of the vessel.
4. Impregnate the tissue with a 1 per cent. solution of nitrate of silver to which is added, at the moment of use, 10 per cent. of pyridine. A considerable volume of this mixture should be employed and the tissue should be kept in it, in a stoppered bottle, for two or three hours at room temperature and, subsequently, at a temperature of about 50°C. for from four to six hours. The length of time for which the tissue is allowed to stand in the silver solution depends upon its permeability.
5. Wash rapidly in some 10 per cent. solution of pyridine.
6. Reduce in a 4 per cent. solution of pyrogallic acid, adding, at the moment of using, 10 per cent. of pure acetone and 15 per cent. (of the total volume) of pyridine. Reduction will be complete at the end of some hours.
7. Dehydrate in alcohol, clear in xylol and imbed in paraffin in the usual way.

In the latter method Levaditi recommends, if counterstaining is required, the use of Unna's polychrome methylene blue, or toluidine blue, followed by differentiation with Unna's glycerine ether.

The advantages which Levaditi claims for the latter method are two, the shortening of the time for which it is necessary to leave the pieces in the silver solution and the greater number of spirochetes which are demonstrated. The latter state-

ment is, doubtless, correct, but, in the tissues of a syphilitic foetus which I had the opportunity of staining by the former method, the spirochetes were demonstrated in such enormous numbers that it was hard to conceive that any remained uncoloured. With regard to the alternative methods of counterstaining, mentioned above, such a procedure is hardly necessary ; the results are never very satisfactory and the chief histological details are sufficiently brought out by the silver process to allow of the relationship between the spirochetes and the tissues being studied. The reasons for the comparatively poor results obtained by counter-staining are, partly, the action of the various solutions upon the tissues, and, partly, the degenerative changes which the tissues have undergone. A curious fact observed by Leishman, in this connexion, is that the tissue in the immediate neighbourhood of the aggregations of spirochetes appears to take the nuclear stain much better than the areas which are free from spirochetes. It would almost appear as if the spirochetes tend to collect and multiply in the zones which are freest from degenerative change.

Another method of silver staining has been recommended by Petresco ; in this the tissue is hardened in absolute alcohol for 48 hours and subsequently put into silver solutions of gradually increasing strength ; the sections are examined rapidly and only exposed to the action of light for as short a time as possible, in order to avoid the reducing action of the light. The method does not appear to present any advantages over that of Levaditi.

Ravaut and Ponselle have suggested the application of Levaditi's method to the investigation of the presence of spirochetes in the blood. They advocate the dropping into water of the blood to be tested, the collection of the fibrinous clot which results, and its subsequent treatment as a piece of tissue by Levaditi's method. In this manner they

claim that spirochetes may be detected even when present in very sparse numbers. Others have not, however, been so fortunate.

Differentiation of the Spirochaeta pallida from other Spirochetes.—As already mentioned, *Sp. pallida* is an extremely delicate, flexible spirochete with closely set, deep and regular spirals, which moves across the microscope field so languidly that it is easy to keep it in view for many hours. In films it is difficult to stain, maintains the regularity of its spirals very faithfully and is stained a delicate rose tint when treated with Giemsa's or Leishman's stain.

By these characteristics it is easily distinguished from all other spirochetes with the exception of *Sp. pertenuis* (of Yaws), *Sp. microdentia* (found in hollow teeth) and *Treponema mucosum* (lately isolated by Noguchi from cases of pyorrhoea alveolaris).

It is easy, however, for the beginner to apply many of the above characteristics to other very delicate spirochetes frequently seen in specimens taken from chancres, condylomata and other ulcerating lesions if, as is now customary, he relies for his diagnosis entirely on examination by dark-ground illumination, and mistakes are frequently made by untrained observers. The beginner who has nobody to correct his diagnosis is advised, therefore, to get his eye accustomed to the appearance of *Sp. pallida* by examining the exudate from syphilitic papules, since in this situation *Sp. pallida* occurs alone and the observer is on certain ground.

Spirochaeta pertenuis is indistinguishable morphologically from *pallida*. Fortunately this is not of great practical importance, since Yaws is a disease of limited geographical distribution.

Sp. microdentia and *Treponema mucosum*, which cannot be distinguished morphologically from one another, are found in lesions about the teeth, and therefore not in situations

usually occupied by syphilitic mouth lesions. They are thinner and shorter than *Sp. pallida* and stain quite easily, so should cause no difficulty.

In exudate from chancres and condylomata occur other spirochetes of all gradations of thickness, regularity and depth of spiral. At one end of the scale is *Sp. refringens*, a very coarse wavy spirochete which is not the least like *Sp. pallida*. Perhaps next is *Sp. balanitidis*, a short, fairly thick spirochete with fairly regular but shallow spirals. In fresh preparations it darts across the field at a great speed, its whole length quivering so rapidly that it is almost impossible to distinguish its spirals. *Sp. gracilis* is still finer than these, but about twice the thickness of *Sp. pallida* ; it has closely set spirals, but its movements are very awkward in comparison with those of the specific organism. It is generally this variety which an observer who has not seen *Sp. pallida* for some time is apt to mistake for the latter. When the two spirochetes are alongside one another it seems incredible that they should be confused ; the fact is that it takes some time for a worker to realize how very fine is the micro-organism of syphilis. *Sp. refringens, balanitidis* and *gracilis* all stain much more easily than *Sp. pallida*, do not retain the regularity of their spirals so faithfully, and when treated with Giemsa's or Leishman's stain take on a blue or deep purple tint. All of them are surface organisms, and rarely occur in specimens prepared from sores which have been well cleaned beforehand.

A spirochete found in ulcerated carcinomata was called by Mulzer "pseudopallida." It is probably included in those described above and bears no resemblance, in fresh preparations at any rate, to the organism of syphilis.

CHAPTER IV

THE SERUM DIAGNOSIS OF SYPHILIS

Amongst the great advances in the diagnosis and treatment of syphilis which have been made in recent years, probably none surpass in importance the serum diagnosis.

The long periods of clinical latency which specially characterize this disease, with the consequent danger of lulling the patient into a false sense of security, and the frequently terrible manifestations which may follow neglect of treatment, have made the management of syphilis a particularly difficult matter. To convince the patient that he is still suffering from syphilis is half the battle of persuading him to continue treatment when clinical signs are absent. It is in this that the Wassermann serum test has proved particularly valuable. Though it does not enable us absolutely to affirm the absence of syphilis, it affords us a clearer insight into the real condition of a patient who has at some time been infected with syphilis than we could ever obtain by reliance on clinical signs alone. It enables us to estimate more closely the relative values of different lines of treatment, and by affirming the presence of syphilis in clinically obscure cases it frequently indicates a line of treatment which might not otherwise be attempted.

Before describing the technique of the test it is necessary to explain briefly the terms used and the theoretical foundation on which it is based. To do so will require a short discussion of some processes of immunity.

Generally speaking, when a foreign proteid, e.g., pathogenic bacteria, toxin, cells or serum of another animal, etc., gains entrance, artificially or otherwise, into an animal's blood stream, the invaded animal develops a resistance to the introduced proteid. A good example of this is the immunity which is induced by an attack of typhoid fever or an injection of typhoid vaccine. Analysis of the immune animal's blood reveals the fact that substances which are antagonistic to the foreign proteid have appeared for the first time, or if they were present before have increased very markedly. These antagonistic substances are known generally as antibodies, and the foreign proteid whose introduction into the animal stimulated their production is known as antigen.

Antigen therefore is any foreign proteid the introduction of which into the body of an animal gives rise to the formation in that animal's blood serum of antibodies. We will discuss here only such antigens as foreign blood cells and bacteria, and amongst the antibodies to which they give rise only those which when mixed with such blood cells or bacteria as caused their production have the property of dissolving them. These antibodies are known as haemolysins or bacteriolysins, according to whether their respective antigens were foreign blood cells or bacteria.

After injecting such an antigen as the red blood cells of a sheep into a rabbit in suitable doses and at correct intervals, the rabbit's blood-serum develops the power of dissolving sheep's blood cells, causing the haemoglobin to diffuse out into the medium. Thus a suspension of sheep cells in physiological salt solution is turbid and if allowed to stand the cells sink to the bottom, leaving the supernatant fluid clear and colourless. But if rabbit's *fresh* anti-sheep-cell serum is added to it in suitable quantities, and the mixture is incubated, it quickly becomes transparent and bright red, while no deposit forms.

Further analysis shows that if the same anti-sheep-cell serum is heated at 55°C. for, say, half an hour, or is allowed to stand for a number of days, it loses its power of dissolving sheep cells. If such heated or stale anti-sheep-cell serum is added to sheep cells no apparent effect is produced, even under examination with a microscope. Nevertheless the anti-sheep-cell serum does produce an effect on the cells, since if to the mixture is added any fresh unheated serum, which by itself has no effect on sheep cells, solution of the red cells (haemolysis) occurs.

It is clear from this that haemolysis is the result of two substances acting on red cells, neither of which is able to act without the other. One disappeared when the serum was heated or was allowed to stand for some days, but is evidently present in every fresh serum. This is known as complement. The other, which was not destroyed by heating or on standing, but is not present in every serum, being developed by the injection of foreign blood cells, is known as amboceptor.

Amboceptor is specific to the antigen which stimulated its production. Thus if anti-sheep-cell amboceptor is added to the red blood cells of a horse together with fresh unheated serum (complement), no haemolysis results. The specific nature of amboceptor and the non-specific nature of complement are well illustrated by the analogy of Fischer. The blood cells are a highly intricate lock, their specific haemolytic amboceptor is the key which fits the lock, and complement is the hand which turns the key. Any key will not fit the lock, but any hand will turn the proper key when it is fitted.

For all practical purposes it may be said that in the process of immunization it is only the amboceptor, not the complement, which increases in quantity.

The blood serum of many animals contains naturally some haemolytic amboceptor; thus fresh human serum will dis-

solve sheep cells and the serum of some guinea-pigs will dissolve ox cells.

The interaction between an antigen, its specific amboceptor and complement results in the destruction of complement. This was proved by the Bordet-Gengou phenomenon, which is the theoretical foundation of the Wassermann test, and is briefly as follows. If an animal be immunized against a given bacterium (antigen), and its heated blood-serum (containing amboceptor which is specific to that antigen), the antigen and any fresh serum (complement) be mixed together in *suitable* proportions and incubated at 37°C. for, say, half an hour, and if then the mixture be tested for the presence of complement, none will be found. The test for free complement will be suggested by what has already been written. It will be remembered that the addition of heated anti-sheep-cell serum to sheep's cells produced no visible effect, but that the further addition of complement resulted in solution of the red cells (haemolysis). Obviously therefore a mixture of sheep's or other animal's blood cells and its specific amboceptor is a very convenient reagent to use in testing for the presence of free complement. A suspension of blood cells with their specific haemolytic amboceptor is known as a suspension of sensitized cells. If such a reagent be added to the above mixture of bacteria (antigen), their specific amboceptor and complement after incubation, no haemolysis will occur, proving the absence of free complement. If, however, bacteria and an amboceptor which is not specific to those bacteria (e.g., cholera vibrios and anti-typhoid serum) and complement be incubated together and the test for free complement (addition of sensitized cells) be applied, the haemolysis which results proves that an antigen will not bind nearly as much complement in the absence of its specific amboceptor.

From what has been said it will be easy to understand

how a given fluid can be tested for the presence of any proteid or, on the other hand, for any antibody. All that is required to test for a given proteid is an antibody to that proteid and some fresh serum (complement), and in testing for an antibody the requirements are the antigen and some fresh serum. If the complement is bound in the mixture of the tested fluid, known antigen, and complement, then the suspected antibody is present.

Instead of the bodies of micro-organisms it was found that watery extracts of these could be used as antigen, and this led Wassermann and his collaborators to conceive the idea of testing the serum of syphilitics for antibody to *Spirochaeta pallida.* Cultures of this micro-organism were not available, but the liver of an infant dead of congenital syphilis is generally so stuffed with *Sp. pallida* that it is practically a rich culture, and it was considered that a watery extract of such a liver would act as *Sp. pallida* antigen in the test. The result justified the hopes of Wassermann, Neisser and Bruck. Syphilitic serum (believed to contain antibody to *Sp. pallida*), extract of syphilitic infant's liver (believed to contain *Sp. pallida* antigen) and fresh normal serum (containing complement) when incubated together in suitable quantities and then tested for free complement by the addition of sensitized cells, were found to behave in the same manner as in the Bordet-Gengou phenomenon, absence of haemolysis proving that the complement was bound.

The experiments of Wassermann and his colleagues were quickly confirmed by others. It was found that the test is practically specific to syphilis and the Wassermann-Neisser-Bruck reaction became an established factor in the diagnosis of syphilis.

So far the reaction was conceived as a Bordet-Gengou phenomenon applied to the detection of *Sp. pallida* antibodies in the blood serum and, *ipso facto*, to the diagnosis of syphilis.

But it was quickly shown by Levaditi and others that alcoholic extract of not only syphilitic but of normal infant's liver, of guinea-pig's heart and liver, human heart and liver, and of solid organs of other animals, would act as "antigen" in this test for syphilis. Clearly this was a departure from the principles of the Bordet-Gengou phenomenon, because such extracts of normal organs could not contain true *Sp. pallida* antigen, and if they were not true antigen then the substance in syphilitic serum with which they united to bind complement could not be true antibody to *Sp. pallida*. The question whether such true antibody does exist in syphilitic serum or not cannot be discussed here. It is sufficient to state that although the test as it is conducted in the great majority of laboratories (using an alcoholic extract of some solid organ as "antigen") does not detect *Sp. pallida* antibody, yet for practical purposes it is specific to syphilis.

Technique of the Wassermann Reaction.—It will be understood from what has already been written that the requirements for the Wassermann test are as follows: (1) serum to be tested, (2) a serum containing complement, (3) an extract of some suitable solid organ, and (4) a suspension of sensitized cells, the haemolytic system which is required to test for free complement after (1), (2) and (3) have been incubated together. In addition to these, test-tubes, an incubator regulated to 37°C., pipettes, watch-glasses and a supply of fresh, sterile 0·85 per cent. salt solution are also required.

The technique employed by different workers may be divided broadly into two classes: (*a*) the original, and (*b*) modifications designed to simplify the test. By the original test is meant one in which the principle of the original technique in so far as the constituents (1), (2), (3) and (4) above, are derived from different sources, is adhered to. Strictly speaking, most workers now employ a technique which is a

modification of the original technique, though adhering to the above principle; but under modifications is meant here those tests in which the worker relies on the tested serum containing the necessary complement and haemolytic amboceptor, or only the complement.

Original Test—Preparation of the Reagents—Serum to be Tested.—The blood for this may be drawn off into a Wright's capsule just as if required for a Widal reaction. But for a fair test it is necessary to take 1 c.c. of blood, and it is much easier and less painful to draw the blood from a vein at the bend of the elbow. A needle of fairly wide bore (such as is supplied with a 10 c.c. antitoxin syringe) is sterilized by boiling, or immersing it in a pot of olive oil which is heated till it just begins to smoke. A rubber band is fastened round the upper arm of the patient so as to make the veins stand out well, and the skin over a prominent vein is sterilized by painting it with tincture of iodine, or a solution of iodine in chloroform (1 in 15). The needle is held about its middle with its bevel looking upwards and run into the vein. The blood is received in a clean test-tube. It is not necessary for the test-tube to be sterile, unless the serum has to travel for some days to a laboratory. In this case it is best to sterilize the test-tube by steaming it rather than by dry heat, since the blood-clot separates better in a steamed than an absolutely dry tube. The amount of blood which is drawn off is not very material, within limits; as it is easier to work with larger quantities one usually takes about 10 c.c. The blood is set on one side for an hour or two to allow the clear serum to separate. If the specimen has to be sent through the post to a laboratory it is by far the best practice to send only serum, since this does not travel well in contact with clot.

After the clear serum has separated its complement must be removed, by heating it at 55°C. It is usually recom-

mended to heat for half an hour, but I think this is too long a time. The serum loses some of its reacting power at a temperature of 55°C., and this loss increases with the time during which the serum is heated. As I have found that ten minutes at 55°C. is sufficiently long to inactivate 0·5 c.c. (the quantity prepared for the test) of serum, I never heat beyond this time. Some workers remove the complement by treating the serum with barium sulphate, but the technique is more complicated and will not be described. It was at one time recommended to use active serum so as to avoid the loss of reacting power which results from heating. Such active serum generally reacts more strongly, but must be used in smaller amounts than are employed with heated serum; otherwise normal serum will often give a positive reaction. The varying amount of natural complement, too, which remains in the serum is a disturbing factor, so that altogether it is better to choose the lesser evil and inactivate the serum.

Complement is contained in practically every fresh serum, but some of these contain other elements which are disturbing to the test and others do not contain much complement, so that for the original test it is the common practice to use guinea-pig serum. The blood can be obtained from the ear if required for only a few tests, but it is simpler to bleed the animal to death. After clipping away the hair from the front of the neck the animal is held out over the mouth of a wide glass funnel which leads into a glass vessel, and its throat cut with a razor.

Browning and Mackenzie recommend that guinea-pig serum should not be used till it is over eighteen hours old, as they have found younger serum unduly sensitive to deviation. I have not experienced this and prefer to use it when four to eight hours old; if left for eighteen hours it sometimes loses some of its power. As complement deteriorates with age at room tem-

perature or in the ice chest, the surplus over that which is required for a batch of tests should be kept frozen. For this purpose during the past three years I have employed the following plan. The serum is pipetted off into small capsules, such as are used for vaccine, and these, in turn, are placed in a test-tube, which is capped and immersed in a freezing mixture within a vacuum flask, such as a Thermos. In a good flask it will keep frozen hard for two or three days, but should be examined daily and the freezing mixture renewed as required. The serum should be kept frozen quite hard or it will deteriorate.

Extract ("Antigen").—Originally this was prepared by extracting with salt solution the livers of infants dead of congenital syphilis. Very few now use a watery extract, as syphilitic liver must be procured for it, and such extracts, too, are apt to deteriorate suddenly. Serviceable alcoholic extracts, on the other hand, can be made from a variety of solid organs and are very stable. Whether alcoholic extract of syphilitic infant's liver gives better results than similar extract of normal organs is still much discussed. Browning and Mackenzie hold that syphilitic liver extract contains undesirable constituents and is not so good as extract of healthy organ. I have obtained as good results from extract of normal organs as from syphilitic, and have also found that syphilitic liver extract may be haemolytic and unduly anticomplementary, both of these being undesirable qualities.

Of organs which may be employed for making extract are the following: human liver and heart, ox-liver and heart, guinea-pig's liver and heart, and rabbit's heart. It is impossible to say which of these is the best. As illustrating the difficulty of deciding, the best extract I ever made was prepared from a normal infant's liver, while an extract from another apparently normal liver had to be rejected for its undesirable qualities. Ox-liver has not given

such good results in my hands as guinea-pig's heart, but it is quite possible that with another ox-liver I might obtain much better results.

The usual method of preparing an alcoholic extract is as follows. The organ is minced and then rubbed up in a mortar containing some broken glass with four times its weight of 96 per cent. alcohol. The mixture is put into a bottle and kept at room temperature, with frequent shaking, for twenty-four hours, after which it is filtered through fat-free paper. I have obtained excellent extracts by the following plan. The ground-up mixture of organ and alcohol is kept at room temperature for three days and at 37°C. for three days, being frequently shaken; it is then heated at 60°C. for an hour and filtered through fat-free paper. The filtrate should be quite clear; on standing a deposit settles to the bottom of the bottle in which it is kept, and the extract should not be used till all the deposit has settled, i.e. for about a week.

The above are the simplest methods of preparing extract and generally prove quite satisfactory. Some extracts prepared in this way, especially if autolysed organ is used, may have to be rejected because they are haemolytic and by themselves absorb an undue amount of complement. It has been found by Noguchi and others that these undesirable properties are due to the presence of substances which are soluble in acetone, and some workers use acetone in the preparation of their extracts. The details of some of these methods, which are rather more complicated, are given in Appendix II.

Sometimes, although it has no undesirable qualities such as the above, a simply prepared extract does not act very powerfully with syphilitic serum. Such an extract, of course, would give an undue proportion of negative reactions and would ordinarily be discarded. Sachs has found that such an extract is improved by adding to it 1 per cent. alco-

holic solution of cholesterin. The correct amount is found by trial and varies from 0·3 to 0·5 c.c. of cholesterin solution for every 5 c.c. of the extract. I have found the addition of cholesterin to be an advantage as claimed by Sachs.

Artificial Extracts.—Many chemical substances will deviate complement when incubated with syphilitic serum. Amongst these are lecithin, oleate of soda, taurocholate of soda, glycocholate of soda and oleic acid. Sachs and Rondoni suggested that a combination of some of these would work in place of crude extract and be more uniform. Their artificial antigen was found, however, to be not so good as crude extract and no more uniform. Of all artificial preparations, I have found the ox-liver lecithin and cholesterin mixture of Browning and Mackenzie to be the most reliable. The details of its preparation are given in Appendix II.

The Haemolytic System.—This is a suspension of red blood-cells which have been sensitized by the addition of the heated serum of an animal which has been immunized against those cells. For the original test it is not very material what variety of blood-cells is used. Most workers use sheep's, which are probably most convenient to obtain. Browning and Mackenzie use ox-cells, and Noguchi claims advantages from the use of human cells. Whatever variety of cells is chosen it is necessary to immunize some animal with them, and the most convenient is rabbit. For the sake of convenience we will describe the technique when sheep's cells are used.

The blood is usually obtained at the slaughter-house. It may either be received into a 1 per cent. solution of citrate of soda in physiological salt solution or into a bottle containing a number of glass beads. The bottle, etc., should be sterile, and it is best to collect the blood after the sheep has bled for some time, as the first blood to flow must wash down many micro-organisms from the wool. If beads are

used, as soon as the bottle is half full it is stoppered and vigorously shaken so as to whip the blood in it. It is best to keep the blood in the bottle and to wash it as required for the test or for immunizing purposes. As a rule it keeps good in the cold for three or four days. For use it is necessary to remove the serum from the blood. The blood is placed in a centrifuge tube with an equal quantity of 0·85 per cent. salt solution and spun till the cells are all deposited. The clear supernatant fluid is removed and replaced with salt solution, and this operation is repeated not less than five times. After the last washing the supernatant salt solution is removed and the deposit suspended in salt solution so as to make a 10 per cent. suspension of cells. The strength of the suspension which is used in the test is 5 per cent. and this is obtained by mixing the 10 per cent. solution with an equal quantity of a suitable dilution of haemolytic amboceptor. For titration of haemolytic amboceptor (see later) the strength of the suspension is made 5 per cent. at once.

To obtain the haemolytic amboceptor a rabbit is injected repeatedly with washed sheep cells. It is best to immunize a number of rabbits at the same time, since some may die, and in any case rabbits vary very considerably in their response to the injections—some rapidly producing a potent serum and others the reverse. The injections may be made intravenously (into the marginal vein of the ear) intraperitoneally or subcutaneously. For intravenous injections it is not advisable to give more than 2 c.c. at a time, and if the suspension is too strong (e.g. 50 per cent.) the rabbit may die suddenly about the fourth or fifth injection. I have obtained excellent haemolytic amboceptor by giving six intravenous injections each of 2 c.c. of a 5 per cent. suspension at weekly intervals. As a rule intraperitoneal injections should be stronger and in increasing doses, 2, 5, 7, 10 and 15 c.c. at weekly intervals. Subcutaneous injections are

apt to result in abscesses, but, these avoided, a potent serum can easily be obtained in this way.

After a few weeks the rabbit's serum should be titrated for haemolytic amboceptor in the manner to be described, and when sufficiently potent (usually about ten days after the sixth injection) the rabbit is bled to death. The blood can be collected in various ways, of which the most convenient are the following.

Under ether anaesthesia the skin is reflected from the front of the chest and after searing the site of the proposed puncture with a glass rod the point of a chambered pipette is run into the right heart. The blood is aspirated into the chamber of the pipette, which is emptied into a sterile flask. Or the blood may be drawn off with a syringe, or through a needle and rubber tube attached to a vacuum flask. When as much blood as possible has been obtained in this way the chest is opened, the heart and lungs removed, and the remainder of the blood and clot transferred from the thoracic cavity to the flask. Another method which works excellently is to expose the carotid and strip it down as far as possible after ligaturing it in two places above. The end is then turned into a sterile test-tube and snipped with a pair of scissors.

The blood is set on one side for twenty-four hours before the serum is removed, but when it has clotted the clot should be separated from the sides of the tube, or flask, in which it is contained, so as to allow it to shrink properly.

When the clear serum has separated it is convenient to bottle it in 1 c.c. vaccine ampoules. Every care should be taken to prevent contamination. After bottling, the complement should be removed by heating the serum for half an hour at 55°C. The serum will maintain its potency for many months, but should be kept in the ice chest.

Standardization of the Reagents.—It must be remembered that extract alone and serum alone, as well as normal

serum in combination with extract, will deviate a certain amount of complement. The distinguishing characteristic of syphilitic serum is that in combination with extract it will deviate more complement than any of these. Another point to remember is that some syphilitic sera, especially those of well-treated cases, will not deviate much more complement than will normal sera under the same conditions. It follows from this that the proportions which the respective ingredients bear to one another in the test must be such that, on the one hand, no normal serum will react positively nor, on the other, an undue proportion of syphilitic sera give a negative reaction. On this account, after fixing arbitrarily the amount of the patient's or control serum to be used in the test, it is necessary to estimate quantitatively the strength of each of the other reagents, and from the information thus obtained to fix the amounts of these to be used.

In describing the technique of standardization and the actual test I propose to make a departure from the usual practice of expressing values in c.c.'s and fractions thereof by speaking of volumes in varying dilutions. Thus if in the usual nomenclature the minimum haemolytic dose of complement for 1 c.c. of sensitized cells were found to be 0·02 c.c., I should describe it as 1 volume of a 1 in 50 dilution for 1 volume of sensitized cells, or, briefly, as 1 in 50. Since it is the proportions which matter, and not arbitrary quantities, this amounts to the same thing. The actual size of the volume does not matter within limits, but, chiefly for the sake of economy, in my own practice I have fixed the size of the volume at 100 c.mm. and keep a fairly large supply of capillary pipettes, which are graduated with mercury in the laboratory, to measure this amount. When in use an india-rubber teat is applied to the barrel of the pipette, and with a little practice volumes can be measured and delivered at great speed. In addition to these small pipettes I have a few cham-

bered pipettes which have been graduated with mercury to measure 400 c.mm., or four volumes. This is for convenience in making dilutions.

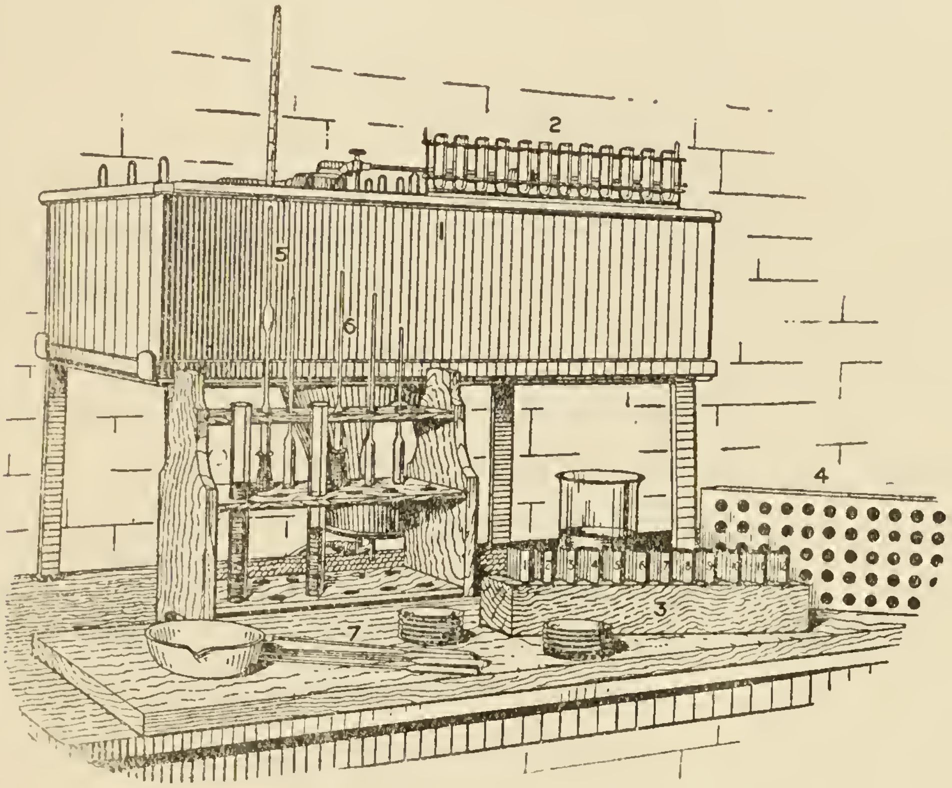

FIG. 5.—Apparatus for the Wassermann Test.

1. Thermo-regulated water-bath.
2. Test-tube rack to fit into water-bath.
3. Test-tubes arranged in block of wood.
4. Block of wood suitable for test-tube stand.
5. Four-volume chambered pipette.
6 and 7. One-volume capillary pipettes.

Using such small quantities of reagents, the various tests can be carried out in test-tubes measuring 5 × 1 centimetre. Instead of the usual type of incubator it is very convenient to have a water bath fitted with trays into which the test-tubes are slipped. In the actual test this saves removing the tubes from the incubator for the addition of sensitized cells.

Titration of Haemolytic Amboceptor.—To ascertain the minimum amount of rabbit's anti-sheep-cell serum which is sufficient to haemolyse completely a volume of sheep cells with the help of an excess of complement, a number of small

test-tubes are set out in a row and into each is placed one volume of a 5 per cent. suspension of the washed sheep cells. A series of dilutions of the anti-sheep serum is prepared, e.g. 1 in 125, 250, 500, 750, 1,000, 1,500, 2,000, and from each of these dilutions in turn a volume is taken and added to the sheep cells in one of the tubes so that the row of tubes now contains a series of equal quantities of sheep cells in contact with varying amounts of haemolytic amboceptor. After half an hour one volume of a 1 in 10 dilution of fresh guinea-pig serum (containing complement) is added to each of the tubes and all are placed in the incubator at 37°C. The tubes are shaken about every ten minutes and the reading is taken at the end of an hour. The tube is sought which contains the smallest amount of amboceptor and in which there is complete haemolysis. The dilution of amboceptor serum in this tube represents the minimum haemolytic dose (M.H.D.) of the titrated amboceptor. It is not advisable to work with an amboceptor with a lower titre than 1 in 400. An excess of complement is used since one M.H.D. of amboceptor will not effect complete haemolysis when working with one M.H.D. of complement and, within limits, the larger the amount of amboceptor with which the cells are sensitized, the smaller the M.H.D. of complement. This is mentioned here as it affects the question of the amount of amboceptor to use in sensitizing the cells for the titration of complement and for the test itself.

For sensitizing the cells some workers use 2½, others 4 M.H.D., and still others larger quantities of amboceptor. Whatever quantity is to be used in the test proper must be used in titrating the complement. Since in the test proper the cells come into contact with a small but variable amount of haemolytic amboceptor which is present in the human serum, I have always considered it better to sensitize the cells beforehand with a large amount of amboceptor, so that

in the test proper the M.H.D. of the complement as ascertained by previous titration will not be affected by the additional amboceptor in the tested sera. For this reason I sensitize the sheep cells with not less than 5 M.H.D. of haemolytic amboceptor.

To make up the sensitized cells for titration of complement and for the test, assuming that 20 c.c. of sensitized cells are required and that the M.H.D. of amboceptor is 1 in 1,500, 10 c.c. of a 1 in 150 dilution of the amboceptor is prepared and added to an equal quantity of a 10 per cent. suspension of sheep cells, making 20 c.c. of a 5 per cent. suspension of cells in a 1 in 300 dilution of amboceptor.

Amboceptor is very stable and need not be titrated more often than once in about three months.

Titration of Complement.—Complement must be titrated each time the test is performed to ascertain the amount to be used.

The titration is done in a similar manner to that employed with amboceptor. A series of tubes is laid out and into each is placed one volume of a varying dilution of guinea-pig serum, e.g., 1 in 10, 20, 30, 40, 60 and 80. To each is then added one volume of sensitized cells prepared as above, and two volumes of salt solution, to make the bulk the same as in the test proper. The mixtures are incubated for half an hour and at the end of this time the tubes are examined. As in the titration of amboceptor, the tube containing the smallest amount of complement and in which haemolysis is complete is sought and the amount of complement in it is noted as the M.H.D. of the complement.

The amount to be used in the test varies with different workers. Browning and Mackenzie use as a minimum amount 5 M.H.D. plus the number of M.H.D. which the serum alone and the extract alone will absorb. This seems excessive and likely to give an undue proportion of negatives, especially

with the serum of well-treated cases. McIntosh and Fildes use 2 M.H.D., but they prepare their extract in such a manner that it is not likely by itself to deviate so much complement as when prepared in the manner advocated by Browning and Mackenzie. This method of fixing the amount of complement to be used in the test is better than that advocated by many continental writers of using an arbitrary amount of complement, e.g., 1 in 10 or 1 in 20, since, as Browning and

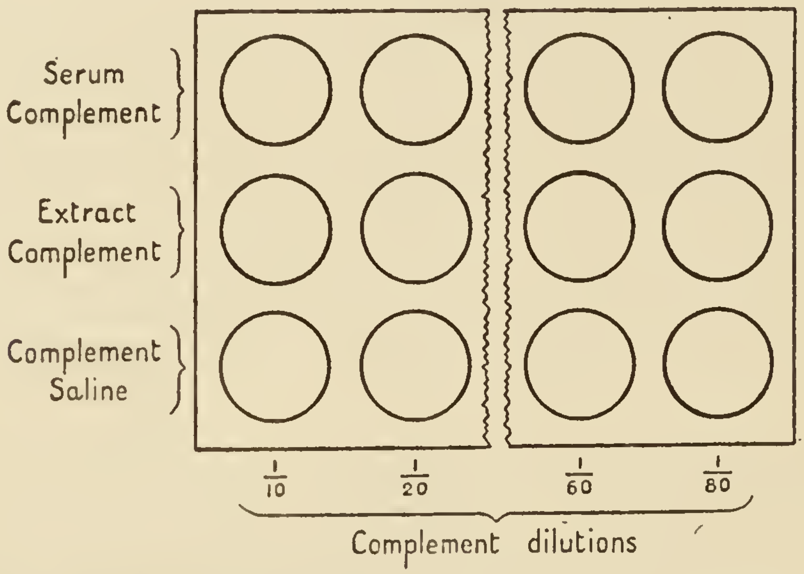

Fig. 6.—Plan of arrangement of tubes for titration of complement and ascertaining the amount of complement absorbed by serum and extract respectively, when acting alone.

Mackenzie have pointed out, the titre of complement in guinea-pig's serum varies so that if an arbitrary amount is used the serum-extract combination may on one occasion be required to deviate 6 and on another only 3 M.H.D. of complement. I now use, as a minimum, 3 M.H.D. of complement. For convenience, if lysis is complete in the 1 in 60 tube, the amount used in the test is one volume of 1 in 20, and if quite complete in the 1 in 40 tube and almost so in the 1 in 60, the amount is fixed at one volume of 1 in 15. Besides this, minimum, amount of complement I set up the same serum and extract with larger amounts of complement, as will be men-

tioned in more detail when discussing the quantitative estimation of the reaction.

In addition to determining the M.H.D. of the complement it should be ascertained how much complement is deviated by the amount of extract to be used in the test and the amount of tested serum, each acting alone. For this two additional rows of tubes are set out (Fig. 6), into each tube of one row is placed a volume of the extract diluted as it will be used in the test, and into each of the other row a volume of any of the sera to be tested, in the same dilution as will be employed in the test. Into each tube of each row is placed a volume of the guinea-pig's serum in the same varying dilution as in the titration for M.H.D. The mixtures are incubated for half an hour, and to each tube is then added one volume of sensitized cells. After incubation for half an hour longer the tubes are read. To take a common example of such a reading, when the M.H.D. of complement is 1 in 60, the highest dilution of complement in the extract row which gives complete lysis is 1 in 30, showing that the extract by itself has absorbed one M.H.D. of complement. In the serum row, using 1 in 5 serum, it is common under these circumstances to find that the tube containing 1 in 40 complement is the last to show complete lysis, showing that the serum alone has absorbed rather less than one M.H.D. of complement. It is not practicable in a large batch of tests to estimate the auto-deviating power of every one of the tested sera, and, in any case, in the test itself the serum is put up with the minimum amount of complement used in the test, so that any abnormal deviating power which may be displayed by a serum acting alone is guarded against.

The Extract varies in its deviating power according to the manner in which it is diluted. If this is done slowly the deviating power is greater than when the dilution is effected suddenly. McIntosh and Fildes recommend quick dilution,

while Browning and Mackenzie advocate gradual dilution so as to obtain the most turbid emulsion possible. Whichever method is chosen should also be adopted in titrating the extract.

I have always diluted the extract in the manner recommended by Browning and Mackenzie. The extract is floated on the top of the necessary amount of saline, just as urine is floated on nitric acid; the tube is set to one side for a time, and a white ring forms at the junction of the two fluids. The

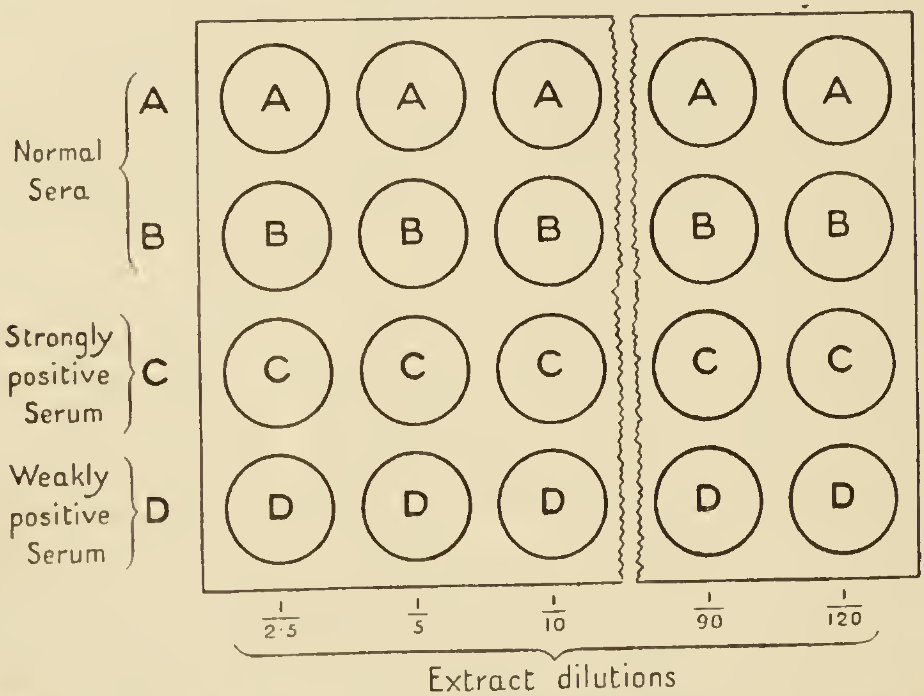

FIG. 7.—Plan of arrangement of tubes for titration of extract.

tube is then rolled between the hands, at first slowly till the salt solution has diffused into the extract lying above, and then more quickly. Finally, when the two fluids are almost mixed, the tube is inverted and the result is a turbid emulsion.

Before titrating the extract it is advisable to ascertain that it is not unduly haemolytic. To do this a volume of a 1 in 5 dilution of the extract should be incubated with a volume of 5 per cent. suspension of cells and two volumes of saline for an hour. If no haemolysis is apparent at the end of an hour the extract is so far satisfactory.

The strength of extract to use in the test is determined in different ways. Many workers use arbitrarily an amount which is equivalent to one volume of a 1 in 5 dilution. McIntosh and Fildes use one-third the minimum amount, which, when acting alone, is just sufficient to deviate completely 2 M.H.D. of complement. The following method, though it takes rather longer, is very satisfactory and has the advantage of estimating the value of the extract. As the titration need be carried out only at the outset and occasionally afterwards, the extra trouble is not of any great moment.

Four rows of test-tubes are set out and may be marked A, B, C and D respectively; each row contains nine tubes. Into each tube of row A is placed one volume of a 1 in 5 dilution of the serum of a normal person. Into each tube of row B a similar amount of another normal serum. Into each tube of row C the same amount of a serum which is known to give a strong Wassermann reaction (generally that of a florid secondary syphilitic). Lastly, into each tube of row D is placed the serum of a patient who gives a feeble Wassermann reaction. A series of dilutions of the extract to be tested is prepared, e.g., 1 in 5, 10, 15, 20, 40, 60, 90 and 120. Into the first tube of each row are placed two volumes of the 1 in 5 dilution of extract; into the second, one volume of the 1 in 5; into the third, one volume of 1 in 10, and so on. In every tube is placed a volume containing three M.H.D. of complement and, to make the bulk equal, a volume of saline is placed in all except the first tubes. After incubating for half an hour a volume of sensitized cells is added to each tube and incubation continued for another half-hour. The tubes are then examined, and the results vary with the quality of the extract. With a good extract all the tubes containing normal serum (Rows A and B) will show complete haemolysis, or, at most, there will be the very least deviation in the tubes containing two volumes of 1 in 5 extract. In the strongly syphilitic

serum tubes (row C) lysis may be complete only in the tube containing 1 in 90 and 120, or even only in the last named. In the weakly syphilitic lysis may be partial in the tubes containing 1 in 10 and higher dilutions of extract. A poor extract may fail to deviate with a strongly syphilitic serum when in a dilution of 1 in 10, and yet show partial deviation with a normal serum when in a dilution of 1 in 5.

The strength of extract to be used in the test is provisionally fixed at half the amount which just fails to deviate 3 M.H.D. of complement when in contact with a normal serum. This amount is then incubated alone with a number of varying dilutions of complement, just as was described in the titration of complement, to ascertain how many M.H.D. of complement it will deviate. If it deviates only one M.H.D. or less, the amount is so far satisfactory.

Finally, before taking it into use the new extract is tested alongside an accredited extract with 20 normal and 20 syphilitic sera.

The Test.—A normal and a known positive serum should be tested with the sera under examination. It is a distinct advantage to estimate the strength of the reaction. Here, again, the practice of different workers varies. Some consider that the strength of the reaction varies inversely with the amount of tested serum which will deviate a constant amount of complement with a constant amount of extract, and use varying quantities of tested serum. Generally this appears to be true, florid cases of syphilis reacting with smaller amounts of tested serum than well-treated cases; but sometimes a given amount of serum will give a negative and half this amount a positive reaction. Others vary the amount of extract, believing that the strength of the reaction varies inversely with the amount of extract which produces a positive reaction. This is certainly a useful method with modifications. In over 3,000 Stern tests I have never found a

serum react with the smaller and yet fail with the larger amount of extract, and in treated cases the reaction with the smaller amount of extract is the first to die out. In the original test, following the practice of Browning and Mackenzie, I have always estimated the strength of the reaction by varying the amount of complement, on the principle that

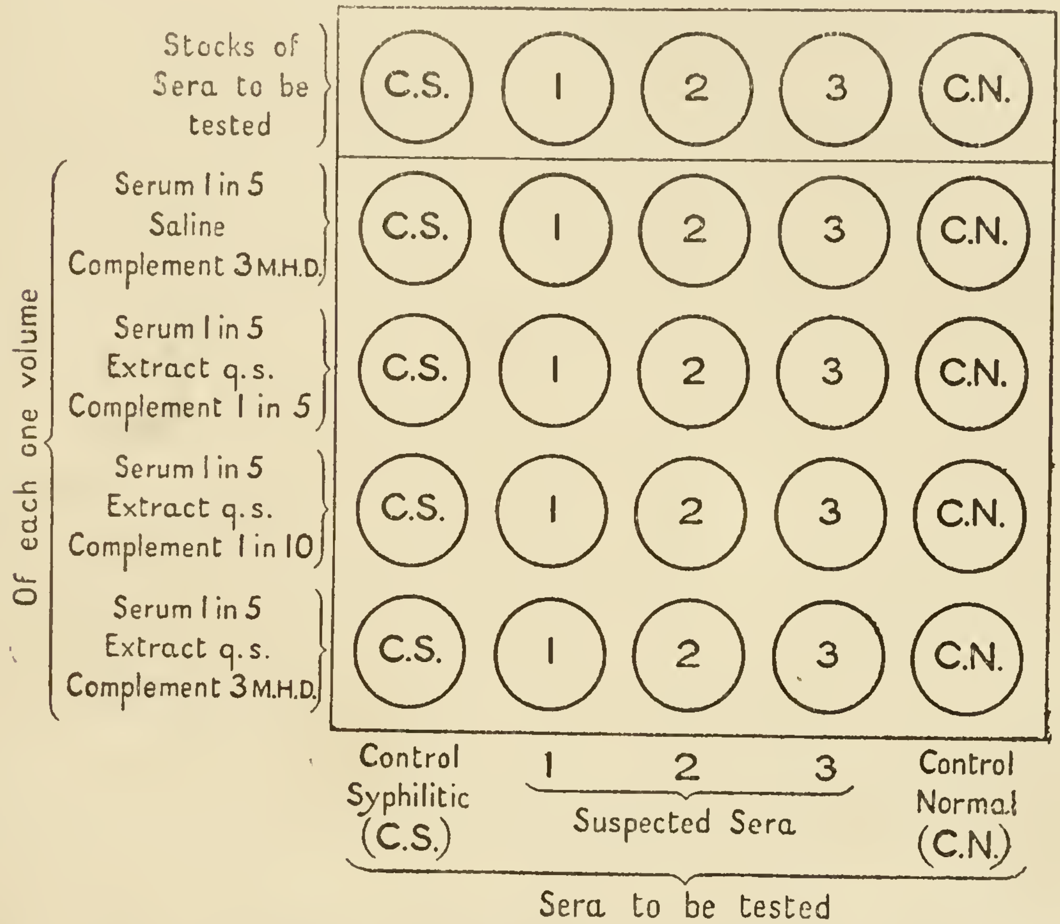

FIG. 8.—Plan of arrangement of tubes for the original Wassermann test when the strength of the reaction is determined by the amount of complement deviated. After preliminary incubation, to each tube is added one volume of sensitized cells.

the stronger the reaction the more complement will be deviated. The results by this method, judging by about 7,000 tests, coincide very closely with clinical symptoms and the effect of treatment.

Assuming that a constant amount of tested serum and of extract respectively are to be used and that to estimate the strength of the reaction three different amounts of comple-

ment are to be used, a block of wood into which five rows of holes have been bored is taken and along the back row are set out the sera to be tested. The front four rows are filled with empty test-tubes, so that, as shown in the plan, there are four tubes in front of each serum. Each serum is taken in turn, diluted to 1 in 5 with 0·85 per cent. salt solution, and one volume of this dilution is placed in each of the four tubes.

When every serum has been dealt with in this way, into every tube of the front three rows is placed one volume of the diluted extract, and, to make the bulk equal in all the tubes, a volume of saline is placed in each of the fourth row tubes.

The complement is next added. Into each tube of the front and fourth rows is placed a volume containing 3 M.H.D. of complement (e.g., if the M.H.D. of the complement is 1 in 60 a volume of 1 in 20 is placed in each of these tubes). Into every tube of the second row is placed a volume containing 4½–6 M.H.D. of complement (generally 1 in 10) and into each of the third row a volume containing 9–12 M.H.D. of complement.

It will be seen from this arrangement that the fourth row differs from all the others in containing no extract. It is a control to show that the amount of serum in each test cannot by itself deviate the smallest amount of complement used in the test.

The tubes are shaken and placed in the incubator in the same arrangement. Using a water-bath and the quantities mentioned it is not necessary to incubate for more than half an hour, though possibly slightly cleaner results may be obtained in a few cases by incubating for an hour.

At the end of this period to each tube is added a volume of sensitized cells, and incubation allowed to proceed. The tubes are shaken every five or ten minutes and if the normal control serum is placed last (as shown in the plan) it is sufficient to take the reading when this shows complete haemolysis. As a rule, the reading can be taken in half an hour.

The following are the rules to be observed in reading the results: (1) Failure of the normal serum test to show complete haemolysis in all its tubes entails rejection of the whole batch of tests. (2) Failure of any tube in the fourth row (control) to show complete lysis entails rejection of the test of the serum of which it is a control. These conditions being satisfied, (3) failure of haemolysis in each of the front three tubes (containing extract) devoted to the testing of any serum may be marked as strongly positive (+ + +). No haemolysis in the front two, but lysis in the third row tube, not so strongly positive (+ +), and no lysis in the front tube only, with lysis in the other two containing extract, just positive (+). Incomplete lysis in a front row tube may be marked as doubtful ($\underline{+}$ or $\underline{\underline{+}}$), and complete lysis in a front tube is returned as negative.

If the test is for diagnostic purposes it is a good plan to retest the serum if the reaction is simply +; this reaction, however, is good enough for a diagnosis. Doubtful reactions, $\underline{+}$ and still less so $\underline{\underline{+}}$ should not be considered diagnostic. Such reactions are, however, generally given by very early or by well-treated cases of syphilis, and an early opportunity should be taken of testing the serum again, no treatment being administered in the meantime unless this is designed to provoke a definite reaction, as will be mentioned later.

Modifications of the Wassermann Reaction.—As mentioned, most workers employ a technique which is in some particular a modification of the original, but by this term we mean here those tests in which, chiefly for the sake of simplicity, the worker relies for the complement and amboceptor, or for the complement alone, on that which is contained in the tested serum. It will be possible here to mention only a few of the numerous modifications which have been devised on these principles. In all of them the serum must be quite

fresh, preferably not more than 24–48 hours old; otherwise its complement may be absent or defective.

Modifications in which the Amboceptor is Artificial, as in the Original Test, but the Complement is contained in the Patient's Serum—Stern's Test.—This test was designed to be used in conjunction with the original.

The original directions were to use the same amount of serum as for the original, but two quantities of extract, respectively two-fifths and one-fifth the amount which is suitable for the original test. The strength of the blood suspension is 2·5 per cent, and the cells are sensitized with 9–12 M.H.D. of haemolytic amboceptor. I have used rather smaller amounts of extract than those originally recommended, viz., one-third and one-sixth respectively the amount used in the original. I have tested a very large number of sera by this method, always in conjunction with the original, and found the following to be a convenient plan of carrying it out.

Each serum is tested in three tubes placed one behind the other. Into each of these is placed one volume of a 1 in 5 dilution of the *unheated* serum. The extract is diluted with saline to make two strengths, respectively $\frac{1}{3}$ and $\frac{1}{6}$ of that used in the test by the original method. Into the front tube is placed one volume of the extract in the stronger of the two dilutions. Into the second is placed one volume of the weaker extract, and into the back tube is placed a volume of saline to make the bulk equal in all. The tubes are placed in the incubator and at the end of half an hour a volume of the 2·5 per cent. suspension of heavily sensitized cells is added to each. Normal and syphilitic control sera must be tested also. In reading the results particular attention must be paid to the back row tubes, containing no extract, and the test of any serum rejected when haemolysis is not absolutely complete in this tube. When no lysis occurs in either of the two extract

tubes the reaction may be considered as stronger than when the tube containing the smaller amount of extract shows haemolysis.

Emery and Birt have each devised modifications which rely on the complement in the unheated tested serum. In each of these modifications the haemolytic system is a suspension of human cells sensitized with rabbit's anti-human serum.

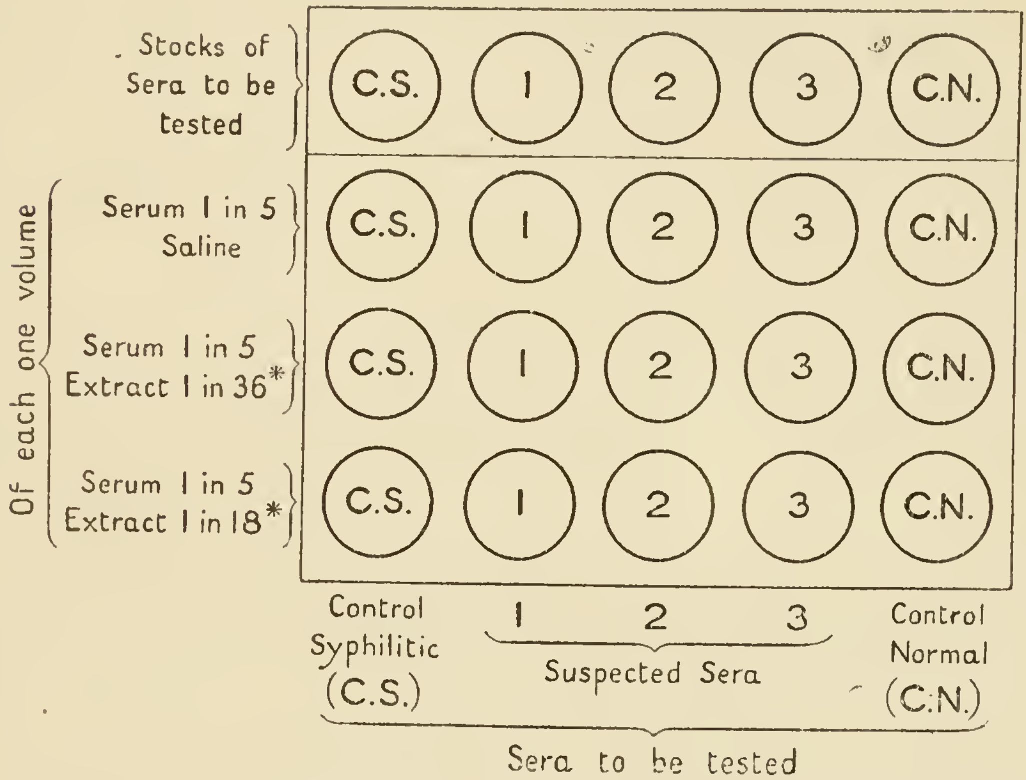

FIG. 9.—Plan of arrangement of tubes for Stern's test. After preliminary incubation, to each tube is added one volume of a 2·5 per cent. suspension of sensitized cells.

* Strength of extract based here on assumption that 1 in 6 is suitable for the original test.

The details of Lt.-Col. Birt's test in his own words are given here by permission.

Human Corpuscle Modification.—This method is that which is most suitable for general use, since the ingredients are stable, and can be preserved indefinitely. A serum diagnosis, therefore, may be made at any time. A description of the process was inserted in the *Journal of the Royal Army Medical Corps* for October, 1910. The substances required are the heart extract which was before described, and a rabbit serum haemolytic to the red blood corpuscles of man. This is prepared

by injecting 10 to 40 c.c. of washed human erythrocytes into the peritoneal cavity of a rabbit at intervals of five days, on three or four occasions. The blood is aspirated from the heart nine days after the last dose. The patient's blood is allowed to remain in the glass capsule in which it is collected from a finger-prick, for four to twenty-four hours, as in previous methods. The clear serum is then withdrawn. The pipette is introduced again into the bottom of the capsule, or into the blood-clot, and such a quantity of red corpuscles is taken up as to make a 5 per cent. mixture when they are added to the serum. One volume of this mixture of serum and corpuscles is put into a tube with four volumes of saline solution, and similar quantities of serum and extract dilutions are placed in other tubes. The fluid in each tube, therefore, contains 1 per cent. of red corpuscles derived from the blood under examination. Thus :—

Tube	1	contains	0·02 c.c. serum and corpuscles and	0·08 c.c. saline.				
,,	2	,,	0·02 ,, ,, ,,	0·08	,,	$\frac{1}{50}$	dilutn.	of ext.
,,	3	,,	0·02 ,, ,, ,,	0·08	,,	$\frac{1}{100}$	,,	,,
,,	4	,,	0·02 ,, ,, ,,	0·08	,,	$\frac{1}{200}$	,,	,,

The tubes are placed in a water-bath at 38°C. for five minutes, or into the 37° C. chamber for half an hour. At the end of this time the red corpuscles are seen lying at the bottom of each tube ; the fluid above them is untinted, as no lysis has occurred. To each tube are now added five haemolytic doses of the rabbit-*versus*-man serum, namely, 0·01 c.c. The tubes are shaken and kept under observation. Lysis will be complete in tube 1 in from three to fifteen minutes. If the blood has been obtained from a non-luetic source, hæmolysis will take place in the extract tubes, though there may be a delay of a few minutes in tube 2, which contains the largest dose. If the blood be that of a patient in the early stage of secondary syphilis, no lysis will occur in any of the extract tubes. The cells fall to the bottom and the fluid remains colourless for twenty-four hours or more. In latent syphilis or if intensive treatment has been adopted, lysis may appear in tube 4 in an hour, and a faint trace may be apparent in tube 3, but the fluid in tube 2 will remain free from colour : a quantitative estimate of the serum is thus made.

Serum placed in each tube is 0·02 c.c., a convenient amount. It may be reduced by one-half if the supply of blood is small. The test can be performed successfully with only 0·2 c.c. of blood, though twice or three times as much is desirable. In any case, blood collected from a prick of the finger is sufficient. Venesection is not necessary.

When practising the test, three series of four tubes are used. The first contains normal serum, the second the serum of a florid secondary case, and the third the suspected serum. Comparison of the last with the other two enables the observer to say to which category it belongs.

Six hundred and twenty-five sera have been examined by this method,

	Total.	Positive.	Negative.	Positive per cent.
Primary syphilis	45	22	23	51
Early secondary syphilis	83	77	6	93
Late " "	103	88	15	85
Latent syphilis	223	127	96	58
Congenital syphilis	5	3	2	—
Ague	6	4	2	—
Scarlet fever	7	4	3	—
Hodgkin's disease	1	1	—	—
Mania	1	1	—	—
Controls, non-luetic	132	Nil	132	—
Failures	19	—	—	—
Total	625	—	—	—

Comparative tests by Wassermann's method were made by Major Harrison in 204 instances. The results agreed 177 times, which equals 87 per cent. In eighteen cases of well treated or latent syphilis the blood gave a positive response to the modification, though negative to Wassermann. In nine the Wassermann was positive, and the modification was negative.

Eighty-five of the specimens of blood were tested by the sheep's corpuscle method. The readings were concordant in 76 per cent. of the experiments. On fourteen occasions the sheep blood reading was positive when the human corpuscle method was negative. These sera were negative when tested by Wassermann's procedure.

The guinea-pig blood modification was applied to 123 of these sera; 89 per cent. of the results agreed. Accordingly the methods confirm one another.

An advantage which the human erythrocyte modification possesses over the former two, lies in the fact that one of the variables is eliminated. In the first two, both the complement and haemolytic amboceptor may fluctuate in amount. In the third process, we add a constant quantity of haemolytic amboceptor. The complement alone varies. Now a minimum dose of complement cannot effect lysis except in the presence of multiple doses of amboceptor. It follows, therefore, that if the quantity of complement in a serum is small, its haemolytic action can still be exerted through the agency of the five units of haemolytic amboceptor added, an influence which is wanting in the first two methods, since the proportion of natural haemolytic amboceptor in human blood is not so high.

The action of human complement on human blood corpuscles which have been rendered sensitive with rabbit-*versus*-man serum is nearly as powerful as that of guinea-pig's. If we take two tubes containing

a 1 per cent. emulsion of such sensitive human erythrocytes, and add to one $\frac{1}{40}$ of its volume of six-hour-old human serum, and to the other a similar quantity of guinea-pig serum, it is often found that lysis is as rapid in the tube which contains the human complement as in the other.

With a fixed number of corpuscles, and a fixed dose of haemolytic amboceptor, the time of lysis is a measure of the complement. Hence arises the necessity of examining the tubes every few minutes after the addition of the haemolytic amboceptor. If lysis is complete at the same time in the control tubes which contain the normal, syphilitic and suspected blood respectively, then the quantity of complement in each is similar, and the readings of the corresponding extract tubes are strictly comparable. The titration of complement, however, can be easily carried out. A ten-fold dilution of the serum in saline fluid is made; 20-, 40- and 80-fold dilutions are prepared from this. One volume of each of these is added to one volume of a 2 per cent. emulsion of human red corpuscles, which have been rendered sensitive by means of five doses of rabbit-*versus*-man serum. The measure of the complement in each tube is therefore $\frac{1}{20}$, $\frac{1}{40}$, $\frac{1}{80}$, and $\frac{1}{160}$ of the volume of fluid, which now contains 1 per cent. of red corpuscles. The period which elapses before haemolysis occurs is noted. Haemolysis is complete in the $\frac{1}{20}$ and $\frac{1}{40}$ tubes within fifteen minutes, if the complement is present in normal quantity, or in other words, the titre of normal human serum is $\frac{1}{40}$. Since the proportion of serum employed in the modifications of Wassermann's reaction is eight times as great—for $\frac{1}{5}$ of the volume of the fluid in each tube is serum—the number of units of complement employed in these processes is eight.

If the blood be examined four to twenty-four hours after shedding, the amount of complement is not subject to great variations. In less than 2 per cent. of the tests by the human blood method has the lysis in the control tube been delayed longer than twenty minutes. Though sufficient complement will have been elaborated at the end of four hours after taking the blood, it will be more convenient generally to perform the test on the following day. There is often still enough complement present at the end of forty-eight hours. It is not unusual to find it existing in small amount in three or four-day-old blood. As an exceptional experience, it was once discovered in human serum which had been preserved for nine days. It is in those cases in which we have not had an opportunity of examining the blood within twenty-four hours of its abstraction, that we scrutinize the rapidity of haemolysis in the control tube. If there is retardation we estimate the deficiency of complement by titration and reduce the doses of extract in like proportion. Consequently the human blood modification admits the same precision as Wassermann's original method.

In both scarlet fever and ague the serum reaction was positive during the attack. It became negative in the convalescent stage.

Of the modifications which rely for both complement and

amboceptor on that which is contained in the tested serum the best known is Hecht's, which has been modified in a few technical details by Fleming. The following is the method of carrying out this test which is adopted by Lt.-Col. Birt.

Alcoholic extract of heart is used. Each serum is tested in four tubes.

Tube 1	contains	0·02 c.c. serum	and	0·08	c.c. salt solution.
,, 2	,,	0·02 ,, ,,	,,	0·08	,, $\frac{1}{50}$ dilution heart ext.
,, 3	,,	0·02 ,, ,,	,,	0·08	,, $\frac{1}{100}$,, ,,
,, 4	,,	0·02 ,, ,,	,,	0·08	,, $\frac{1}{200}$,, ,,

The tubes are put into the incubator for half an hour, or into a water-bath raised to the temperature of 38°C. for five or ten minutes. At the end of this period such an amount of a 5 or 10 per cent. emulsion of sheep cells is added that the fluid in each tube contains 1 per cent. red blood corpuscles. It is important to avoid the addition of an excess of sheep's blood.

Tube 1 must show complete lysis in five or six minutes. In the test of a strongly acting serum all the other tubes show no lysis, while a weakly acting serum shows lysis in all but Tube 2.

Criticism of the Modifications.—In a strictly scientific test of a number of sera for the presence in them of a substance or quality which varies in amount, and when the decision rests on the presence of an excess or a normal amount of that substance, as in testing for the Wassermann substance, it is necessary that all the reagents for the test should respectively be derived from the same source, be in the same amount and be treated in the same way. This principle is, as far as possible, carried out in the original Wassermann test. The amboceptor for all the tests comes from the same source and is used in the same amounts throughout. Similarly with the complement. With the modifications described above it is different. In the Stern, Emery, and Birt tests the complement,

though fairly constant, is an unknown quantity unless the worker takes the trouble to titrate out this substance in each separate serum ; in any case it is possible that the amount in any tested serum may be widely different from that in the controls with which the result is compared ; or it may be more sensitive to deviation, as Browning and Mackenzie maintain is the case with some samples of guinea-pig serum complement, though we have no means of ascertaining this. In the Hecht technique a still further variable is added, since the haemolytic amboceptor is derived from the tested serum. About 10 per cent. of human sera contain no haemolytic amboceptor for sheep's cells.

If there is no lysis in a tube containing extract and serum, while the control, containing serum only, is completely haemolysed, this is recorded as positive. But if a normal serum contained a diminished amount of complement it might show complete lysis in the control tube and none in the extract tube since it must be remembered that extract in the presence of a normal serum will deviate complement, particularly when the serum is unheated as in the case of the modifications.

Certainly the titre of complement in most fresh human sera of the same age does not vary very widely and an additional factor for safety lies in the use of an extremely small amount of extract, but I would not base a diagnosis on a positive reaction to a modification unless I had previously titrated out the complement in both the normal control and the suspected serum.

Even on the score of simplicity, there is no justification for the Hecht test, since anti-sheep serum can be purchased if the worker is not in a position to make it for himself.

The advantage of the modifications lies in their greater delicacy, which probably depends mainly on the fact that the tested serum is not heated. I do not think it possible with safety to make the original test so delicate as the Stern,

for instance. For this reason it is useful to test each serum by a modification as well as by the original. In early cases where for some reason the spirochete has not been found and the patient is under observation, the modification will often give warning to test again at an earlier date than would otherwise be done in routine practice ; this applies also to the observation of patients who have received what is believed to be an adequate amount of treatment. After suspending treatment, if the patient is uncured, the serum will react still earlier to the modification than to the original test, and I think that under these circumstances a positive reaction is sufficient justification to recommence treatment without waiting for a reaction to the original test.

Briefly, a diagnosis of syphilis is a serious matter and should be based on an absolutely reliable test, the original ; over-treatment of a patient is an error on the right side, and is justified by a positive reaction to a test which in a small percentage of non-syphilitic cases may be too delicate.

CHAPTER V

SERUM DIAGNOSIS (*continued*)—EXAMINATION OF THE CEREBRO-SPINAL FLUID—LUETIN REACTION.

Considerable work has been expended in an endeavour to discover the nature of the substance which gives the Wassermann reaction, but the question has not yet been settled. The trend of opinion is that it is a changed albumin, and quite probably it is manufactured by the tissues as a result of perverted metabolism in response to the activity of the *Sp. pallida.* If we may judge from clinical signs and the effect of specific treatment, it is most in evidence in the serum when the *Sp. pallida* is most rampant in the tissues, e.g., in the early secondary stage. An exception to this rule is found in parasyphilis, especially general paralysis, the subjects of which almost invariably give the Wassermann reaction.

Wassermann Reaction in other Diseases.—It would naturally be thought that as the Wassermann substance is not a true antibody it should be found in the serum of patients suffering from other diseases. This has proved to be true, but not to an extent which detracts from the clinical value of the test.

The blood serum of patients suffering from the following diseases has been found by various observers to give the Wassermann reaction : Yaws, Leprosy (chiefly the tuberous variety), Trypanosomiasis, Relapsing Fever, Malaria, Scarlet Fever and Tropical Ulcer. A positive reaction has occasionally been given by the serum of patients *in articulo mortis.* None

of these are conditions which are likely to be confused with syphilis, and a few remarks only are necessary regarding them. Yaws and relapsing fever are diseases due to spirochetes, and the *Sp. pertenuis* of yaws can be distinguished from *Sp. pallida* only by animal experiments. In malaria the reaction has only occasionally been given and then only at the height of the fever. Scarlet fever patients were found by Much and Eichelberg to give the reaction in 40 per cent. of their cases, but this proportion has been found by other observers to be much too high. Counting Much and Eichelberg's 24 cases, McIntosh and Fildes have collected the records of 538 tests by various workers, and the total number of positive reactions amounted only to 28, or 5·2 per cent. The reaction quickly disappears in convalescence.

From the work of Bruck and Cohn it would appear that some extracts give a high proportion of positive reactions in scarlet fever, and others none, both varieties being equally good for deviating complement with syphilitic serum. In tropical ulcer Schüffner found that out of 106 cases 86 per cent. gave the reaction, but only with watery extract; when alcoholic extract was used only 3 per cent. gave a positive reaction.

The Wassermann Reaction in Syphilis.—*Primary Stage.*—It is impossible to give statistics which will convey any idea of the percentage of positive reactions to be expected in this stage. Everything depends on the age of the sore; when this first appears the reaction is almost always negative; when the sore is fifteen days old the majority, and just before the outbreak of the secondary symptoms almost all cases give a positive reaction, provided they have received no treatment. The writer's experience is that when the sore has become indurated a positive reaction may be expected in untreated cases.

It is in the early secondary stage of untreated syphilis that

the highest percentage of positive reactions is obtained; Bruck and Boas give 90 per cent., rather a low figure; McIntosh and Fildes state their belief that 100 per cent. are positive. I have tested 282 cases in this stage which were either entirely untreated or had received less than six mercurial injections, and obtained 96·8 per cent. of positive reactions to the original test; while out of 86 cases tested by Stern's modification 85 were positive. Treatment causes an appreciable falling off in the number of positive reactions, and it is quite possible that some of the cases I have classed as untreated had really been taking "blood mixture" before admission. Secret treatment, however, does not account for all the negative reactions I have obtained in untreated secondary cases. Having repeatedly tested the blood serum of many soldiers, I have records of a few cases which seemed naturally refractory in their response to the Wassermann test and even to Stern's modification. On first admission with well-marked secondary signs, and subsequently when relapses occurred months after any treatment had been given, the reaction was negative, and one can only conclude that it was a peculiarity of these patients that they gave a negative when a positive would be expected.

In later stages of syphilis, with some exceptions mentioned later, the proportion of positive reactions is considerably affected by treatment, and, generally speaking, it varies inversely with the efficiency of such treatment. In compiling Table 1, which shows the results obtained by different workers at various stages of syphilis and in parasyphilis, I have endeavoured to separate untreated from all cases, and the higher percentage of positive reactions given by untreated cases will be seen. The factor introduced by treatment must be taken into account, therefore, in gauging the likelihood of a positive reaction in these stages.

In tertiary syphilis the statistics collected by McIntosh

TABLE I.

Showing the Wassermann Reaction given by the Blood Serum in Different Stages of Syphilis and in Parasyphilis.

Stage.	Collected by McIntosh and Fildes.		Ritz and Sachs.		Army Med. School Lab. U.S.A.		Harrison.	
	Total Cases.	Per cent. Positive.	Total Cases.	Per cent. Positive.	Total Cases	Per cent. Positive.	Total Cases	Per cent. Positive.
Primary	1,133	66·4	120	53·5	578	88·4	367	61·0
Secondary, untreated	269[1]	100	93	98·9	1311	95·8	282	96·8
Secondary, all cases	2,754[2]	90	330	95·7	—	—	652	79·6
Tertiary, untreated	123	99·1	—	—	—	—	—	—
Tertiary, all cases	1,043	83	179	63·7	406	87·4	61	73·7
Latent, untreated	196[3]	72·9	—	—	—	—	—	—
Latent, all cases	3,032	44	1,540	45·5	739	65·8	770	41·5
Congenital	245[4]	95·5	—	—	28	89·2	—	—
General paralysis	440	98	194	86·1	—	—	—	—
Tabes	610	64·4	243	69·5	—	—	—	—

[1] Boas' cases.
[2] Collected by Bruck and Boas.
[3] Mothers of syphilitic infants, who denied infection.
[4] With manifest symptoms.

and Fildes show 83 per cent. positive out of 1,043 cases, their own cases showing 95 per cent. positive.

In the latent stages it is particularly hard to separate the influence of treatment from that of other factors. The most reliable results relate to the mothers of congenital syphilitics who denied knowledge of any infection, since one may suppose that these were untreated. From the carefully collected statistics of McIntosh and Fildes, out of 196 such cases 143 gave a positive reaction. This corresponds very closely with the 75 per cent. of positives which Boas obtained in latent cases which were either badly treated or untreated.

In congenital syphilis with manifest signs almost all cases are positive. In latent congenital syphilitics about 60 per cent. give the reaction.

In parasyphilis the test is applied to the cerebro-spinal fluid as well as to the blood-serum, and the character of the reaction obtained in each of these has an important diagnostic significance which will be discussed later when dealing with the examination of the cerebro-spinal fluid.

In tabes the reaction given by the blood-serum is influenced again by the amount of previous treatment. Thus, Boas found that 100 per cent. of untreated tabetics gave the reaction, but only about 42 per cent. of treated cases.

In general paralysis Browning and Mackenzie obtained a positive reaction in 96 per cent. of their cases. Plaut's cases gave 99 per cent. positive, and Boas obtained 100 per cent. positive in 139 cases. Probably the most valuable work in this connexion is that of Candler and Mann, who give the statistics relating to 109 cases where the diagnosis was confirmed by autopsy. Altogether a positive reaction was obtained at some time in 107, or 98·1 per cent. In five of these the reaction was at first negative and subsequently found to be positive. This illustrates the importance of repeating the test in suspected cases.

The Effect of Treatment on the Wassermann Reaction. —This has been mentioned in explanation of the varying results obtained by different workers, especially in the later stages of syphilis. It is not easy to obtain from the literature particulars which give a reliable idea of the influence of treatment on the Wassermann reaction. With civilians it is difficult to be certain that the patients really take the treatment prescribed, especially if this is in the form of mercury by the mouth or inunctions, unless these are applied by a skilled and conscientious rubber. A great deal also depends on the age of the infection and the amount of previous treatment. In old-standing cases where treatment has been only symptomatic the reaction is particularly difficult, and sometimes impossible, to convert to negative. The same applies to congenital cases,

and unless the author gives full particulars regarding these factors it is impossible to distinguish their influence from that of the treatment.

On this account I venture to show in Tables II and III only the results obtained at Rochester Row with the serum of soldiers who were treated regularly from an early stage of the disease. In Table III the difficulty of converting an old-standing positive Wassermann reaction to negative is partly illustrated by the results obtained with cases which had been previously treated, but in which mercurial treatment had failed to prevent frequent relapses.

When the test is carried out in a quantitative manner the influence of treatment is quickly seen, the reaction becoming weaker in the majority of cases by the end of the first course of intramuscular injections, and during the two years of regu-

TABLE II.

SHOWING THE EFFECT OF MERCURIAL INJECTIONS [1] ON THE WASSERMANN REACTION.

Tested after	Total Cases.	Positive.	Per cent. Positive.
1st course of 6–9 weekly injections . .	95	69	72·6
1st interval of 6–8 weeks	23	16	69·5
2nd course of 4–6 fortnightly injections .	82	43	52·4
2nd interval of 2–3 months	29	20	68·9
3rd course of 4 fortnightly injections. .	83	44	53·0
3rd interval of 3 months	36	20	55·5
4th course of 4 fortnightly injections. .	124	43	34·6
4th interval of 4–6 months	43	24	55·8
5th course of 4 fortnightly injections. .	67	24	35·8
5th interval of 1 month	62	16	25·8
6th or 7th course of 4 fortnightly injections	115	43	37·3
Three months after two years' regular treatment with mercurial injections .	322	135	41·9

[1] Mercurial Cream (Hg gr. i in each), Mercury Salicylate (gr. 1½ in each), or Calomel Cream (Hg_2Cl_2 gr. ⅔ in each).

TABLE III.

Showing the Immediate Effect of Salvarsan, alone or in conjunction with Mercurial Injections, on the Wassermann Reaction (tests not less than two, nor more than six months, after first injection of salvarsan).

		Total Cases.	Previously Positive.	Remained Positive.	Per cent. Remained Positive.	Previously Negative.	Became Positive.	Per cent. Became Positive.	Total Remained or Became Positive.	Per cent. Remained or Became Positive.
Previously untreated (primary and secondary) cases	Salvarsan in conjunction with mercurial injections	153	101	10	9·9	54	3	5·6	13	8·4
	All cases .	257	178	21	11·7	79	7	8·8	28	10·8
Previously treated; chiefly relapses under mercurial treatment	All cases .	191	148	47	31·7	43	5	11·6	52	27·2
Totals of all cases . .		448	326	68	20·8	122	12	9·8	80	17·8

lar treatment by intramuscular injections it is the exception to find cases reacting so strongly positive as untreated cases.

It is rather difficult to explain why it is that in congenital syphilitics, in old-standing, neglected cases and in general paralysis, treatment should have so little or no influence on the reaction. In the two former classes it might be assumed that the spirochetes have become so well-established that it is impossible to destroy them; but spirochetes have not been demonstrated in the tissues of general paralytics, and if the substance in the blood which gives the reaction in paralytics

is the same as that in syphilitics, some other explanation must be sought. It is possible that in response to the long-continued action of the spirochetes the tissues have developed the habit of forming Wassermann substances, and continue it long after the micro-organisms have been destroyed. Certainly in a proportion of these stubborn cases the reaction becomes weaker under efficient treatment, but there are many others on whose Wassermann reaction the most strenuous treatment with salvarsan and mercury has not had the slightest effect, and the future of these patients will be interesting. In the present state of our knowledge, whatever we may hope is the true explanation, it is safer to assume that syphilitics who give a persistently positive reaction are uncured, and to act accordingly.

The Wassermann Reaction in Diagnosis and Treatment.—*In Diagnosis.*—The significance of a positive reaction will be gathered from the above remarks. Excluding a few conditions which have been discussed and can easily be excluded by other methods of diagnosis, a positive Wassermann reaction to the original test indicates the presence of syphilis.

It is necessary here to caution against the tendency to make the presence of syphilis exclude that of other diseases. A positive Wassermann reaction which happens to coincide with a hammer toe does not imply that the hammer toe is due to syphilis; nor does a positive Wassermann exclude epithelioma of the tongue, possibly engrafted on leucoplakia.

Regarding the significance of a negative reaction, it must at once be said that there is no stage of syphilis in which the percentage of positive reactions is 100, so that a negative reaction can never absolutely exclude syphilis, even in untreated cases, while if anti-syphilitic treatment has recently been administered, a negative reaction is of no value whatever. At the same time, in certain stages the evidence afforded by a negative reaction is very weighty. In cases where the diag-

nosis rests between early secondary syphilis and some other disease, in the absence of specific treatment a negative reaction, especially if repeated once or twice, would be almost conclusive against syphilis. In later stages the value of a negative reaction is not so great, though all the evidence points to the fact that in untreated cases a very high percentage of positive reactions is to be expected here. A negative reaction with the serum and, as will be seen later, with the cerebrospinal fluid in cases of disturbance of the cerebral nervous system, is very strong evidence against general paralysis.

In Treatment.—The value of the Wassermann test in estimaing the effect of treatment in syphilis is very generally recognized. The effect of mercury and salvarsan treatments respectively on the reaction is illustrated in Tables II and III. The difference between mercury and salvarsan as regards their effect in converting the reaction to negative coincides very closely with other facts, clinical and microscopical, which attest the more profound influence of salvarsan on syphilis and shows that the Wassermann test is a reliable guide in estimating the relative values of different lines of anti-syphilitic treatment.

If the test is conducted in a quantitative manner so as to estimate the strength of the reaction it gives very early information as to the chances of the treatment proving successful. Taking, for example, the case of a patient giving a strongly positive reaction and treated with salvarsan, if the reaction is going to become negative it will have changed from the original +++ to ++ or + in two weeks; at the end of three to four weeks it is $\underline{+}$ or $\underline{\underline{+}}$, and in five to six weeks it is completely negative to the original test. If at the end of three weeks it is still +++, one may expect that it will remain positive unless further treatment is administered.

In the majority of cases where the reaction previously positive has been converted to negative, but the disease is really

uncured, the Wassermann reaction becomes positive before the clinical signs reappear, so that the test generally gives warning earlier than clinical signs that the disease is not yet cured.

In deciding the question whether a patient is cured and treatment may be stopped entirely, the Wassermann reaction is useful, but great caution must be exercised when a negative result is obtained. Assuming that the patient is not cured, the more recently treatment has been administered the more likely is the reaction to be negative, and vice versa, so that a negative reaction a year after suspension of all treatment is of considerably more value than one only three months after. It is generally said that a series of three negative reactions at three-monthly intervals, commencing three months after suspending treatment, may be accepted as evidence of cure. In addition to this I always advise patients to have a test once every six or twelve months afterwards for some years. The trouble to the patient is, after all, trifling, and the test has not been long enough in use to enable us to fix an absolute standard of cure; it is well therefore to keep on the safe side.

A negative reaction may have its value enhanced by administering a provocative dose of salvarsan (0·1–0·2 grm.) and then testing the blood after two, six and thirteen days. The assumption is that if spirochetes are still present the dose of salvarsan will stir them to renewed activity, which will be reflected in a positive Wassermann reaction. In a few cases I have seen the reaction converted to positive in this way and have certainly not seen a patient who gave a negative reaction after a provocative injection of salvarsan give a positive reaction later. Our experience is too limited, however, to judge this question absolutely.

Other Serum Tests for Syphilis.—Many other tests have been evolved, chiefly with the object of dispensing with the services of the trained pathologist, but with indifferent

success. Some of them, e.g., the epiphanin reaction, appear more complicated than the Wassermann test; others, like the precipitation of syphilitic serum with distilled water (Klausner) or precipitation of a syphilitic serum on the addition of glycocholate of soda (Porges) and the colour reaction of Schurmann, are not specific to syphilis.

A test which may be found useful under special circumstances is the Hermann-Perutz reaction. According to Jensen and Feilberg, though it does not give such a high percentage of positives as the Wassermann test, it never gives a positive with a negative-to-Wassermann serum, so that it may be used as a preliminary, resorting to the Wassermann test only when the H.-P. reaction is negative. The test, as modified by Jensen and Feilberg, is carried out as follows:—

Two solutions are prepared—

A.	Sodium Glycocholate	2·0
	Cholesterin	0·4
	Alcohol, 95 per cent.	100·0

This may be kept as a stock solution.

B. A freshly prepared 2 per cent. solution of glycocholate of soda solution in distilled water.

Equal parts of solution *B* and a 1 in 20 dilution of solution *A* in distilled water are mixed together, and of the mixture 0·4 c.c. is added to an equal quantity of the serum to be tested in a test-tube. The serum is inactivated by heat beforehand. The tube is then shaken and kept at 22° C. till the following day. A flocculent precipitate indicates a positive reaction.

My limited experience with this test confirms the opinion of Jensen and Feilberg. Ninety-eight sera were tested and fourteen gave a positive reaction. All of these but one were positive to the Wassermann test and this patient was syphilitic. Of the eighty-four sera which were negative to the H.-P. test ten were positive to the Wassermann and seventy-four were negative. Six of the sera which gave a

positive H.-P. reaction were from clinically latent syphilitics.

The tubes were kept at room temperature and the sera were tested both heated and unheated. No normal unheated serum gave a positive reaction, but, on the whole, the unheated syphilitic sera gave stronger reactions.

The Cerebro-Spinal Fluid in Syphilis and Parasyphilis.—Until quite recently the interest in this subject was confined almost entirely to the investigation of the cerebro-spinal fluid in obvious disease of the central nervous system. Lately, however, the controversy over the causation of cranial nerve disturbances which have followed injections of salvarsan has stimulated a more extended research, and it has been found that a large proportion (80 per cent., according to Dreyfus) of patients suffering from late primary and early secondary syphilis show pathological changes of the cerebro-spinal fluid.

A very large proportion of these cases display no clinical symptoms to indicate any change in the central nervous system, or at most this is confined to a headache of greater or less severity. They are nevertheless candidates for subsequent lesions of the central nervous system, and it may sometimes be important from the point of view of treatment previously to examine their cerebro-spinal fluid.

Lumbar Puncture.—This is best performed with the patient sitting on a stool with his head down between his knees and his lumbar region thrust well out If done in bed the patient should lie on his left side with his right shoulder well over and his lumbar region arched out as much as possible. A line joining the highest points of the iliac crests crosses the spine of the fourth lumbar vertebra. Slightly below and to the right of this is the site of election for the puncture.

A needle four inches long and provided with a stilette should be used. Previously it should be thoroughly cleaned and then sterilized by immersion in absolute alcohol, which is

removed just before the operation by immersion in ether. The needle should then be dipped in sterile olive oil to facilitate its passage through the tissues. If the patient is nervous it is well to anaesthetize the area of the puncture by injecting eucaine and adrenalin, or 1–2 c.c. of a 0·5 per cent. solution of novocaine.

The puncture is made almost perpendicularly to the back, with a very slightly inward direction. If the needle does not strike bone after penetrating the skin, it passes on fairly easily for a variable distance till it meets a resistance which is evidently softer than that of bone and is due to the interlaminal ligament. The feeling imparted to the fingers as the needle passes through this is quite characteristic. The first few drops of fluid should be allowed to flow into a separate test-tube, since this portion may contain some blood.

The cerebro-spinal fluid may be tested cytologically, chemically, physico-chemically, and for the Wassermann reaction.

Cytological Examination.—This includes an absolute and a differential count of the cells, just as is done in the examination of blood. The enumeration may conveniently be done with a Thoma-Zeiss haemocytometer, mixing nine parts of fluid with one of carbol-thionin. The measuring and mixing can be done with an ordinary capillary pipette armed with a rubber teat. This is probably a more accurate method than using one of the special bulb pipettes sold for the purpose, since it is easy in one of the latter for leucocytes to adhere to the side of the bulb and very hard to dislodge them with the little bead in the bulb; at any rate, this is a frequent source of error in ordinary blood leucocyte counts. Three or four total ruled areas should be counted and the calculation made in the usual way, remembering that the dilution is $\frac{9}{10}$.

A more convenient apparatus than the Thoma Zeiss is the

Fuchs and Rosenthal's counting chamber, in which a larger quantity of fluid can be examined at one time.

Normal cerebro-spinal fluid contains very few cells. The standard instituted by Plaut which considers any number over 10 per c.mm. as pathological is usually adopted. In syphilitic and parasyphilitic lesions the greatest and most constant increase is obtained in general paralysis, and next to this comes tabes. In early stages of syphilis Dreyfus has found as many as 1,500 per c.mm.

The number of cells, though often in accordance with the strength of the Wassermann reaction, is not necessarily parallel, since a high leucocyte count may coincide with a negative Wassermann, and vice versa. The number of cells, though independent of the strength of the Wassermann reaction, is closely parallel to the precipitable substances, globulins and nucleo-albumins.

The differential count of the cells in cerebro-spinal fluid is effected by centrifugalizing the fluid, spreading a film of the deposit and, after staining, making the proportional count as when dealing with blood. In syphilis and parasyphilis the cells are exclusively mononuclear—lymphocytes for the most part, with some plasma cells and perhaps a few large mononuclears with kidney-shaped nuclei. Lymphocytosis is not, however, diagnostic.

Chemical Tests.—These depend on the precipitation of the protein elements, globulin and nucleo-albumin, by the addition of chemicals. Normal cerebro-spinal fluid contains extremely little protein, so that any amount detected by chemical tests is pathological, though it does not necessarily indicate syphilis. The best known of the chemical tests are the Nonne-Apelt, Ross and Jones and Noguchi's tests.

The Nonne-Apelt consists in the addition to the fluid of an equal quantity of saturated solution of ammonium sulphate. A precipitate in three minutes is considered positive.

A precipitate may form in twenty-four hours, but its significance is doubtful.

In the Ross and Jones test 1 c.c. of the fluid is floated on the top of 2 c.c. of saturated ammonium sulphate, and a positive result is indicated by a clear-cut greyish white film at the junction of the two fluids. The ring should be viewed in the dark with a light from the side. The authors say that in their hands the fluid of a general paralytic, diluted eight times, has given the reaction.

In the Noguchi test one part of fluid is boiled for a few seconds with five parts of a 10 per cent. dilution of pure butyric acid in physiological salt solution. One part of 4 per cent. sodium hydrate is then added quickly and the mixture boiled again. A positive reaction is indicated by a flocculent precipitate forming in the following two hours.

None of these three chemical tests is diagnostic of syphilis or parasyphilis. A positive result simply indicates an abnormally high protein content, which may be significant in a syphilitic patient showing no other signs.

Physico-Chemical Test.—Lange has evolved a test which he thinks is diagnostic of syphilitic or parasyphilitic cerebro-spinal changes. A solution of colloid gold is made as follows. To 100 c.c. of double distilled water is added 1 c.c. of 1 per cent. gold chloride solution and 1 c.c. of 2 per cent. potassium hydrate. The mixture is quickly boiled in a Jena glass beaker with energetic shaking, and to it is then added 1 c.c. of 1 per cent. commercial formalin. The result should be a beautiful red-purple transparent fluid without any tinge of blue in it. A 0·4 per cent. solution of pure sodium chloride in double distilled water is also prepared for the purpose of diluting the cerebro-spinal fluid.

A series of dilutions of the cerebro-spinal fluid is made—$\frac{1}{10}$, $\frac{1}{20}$, $\frac{1}{40}$, and so on, doubling each time, till a dilution of 1 in about 40,000 is reached in the thirteenth tube. One c.c. of

each of these dilutions is placed in a test-tube and to it is added 5 c.c. of the gold solution ; the addition must be made quickly, not in portions.

The tubes are left at room temperature over night and then read. The reaction consists in a precipitation of the gold, which is indicated in its various degrees by a change in the colour of the solution from red to reddish-blue, the minimum, blue-red, violet, dark blue, bright blue, light blue, to complete decolourization with a blue precipitate, the maximum reaction. It is in the dilution at which the change in colour reaches its maximum that, according to Lange, lies the distinguishing characteristic of syphilitic and parasyphilitic fluids. Thus in purulent meningitis the maximum commences at some dilution which is higher than 320, and this applies to normal fluid to which blood has been added. With syphilitic or parasyphilitic fluid, on the other hand, the maximum occurs between the dilutions of 1 in 40 and 1 in 80.

The test is therefore qualitative and quantitative : qualitative in the dilution at which the maximum is attained, and quantitative in the grade of the maximum, blue-red to decolourization. The strongest reactions are given by parasyphilitic fluids, next by cases with very manifest cerebro-spinal syphilis, cases of cranial nerve disturbance, and the weakest by cases of secondary syphilis with nothing more than headache.

If by accident the fluid be contaminated slightly with blood serum the syphilis or parasyphilis reaction is not necessarily spoiled. The maximum indicating the latter occurs between 40 and 80, and is succeeded by another maximum at or beyond 320 due to the blood serum. Two results which I obtained will illustrate this point. A sample of cerebro-spinal fluid was drawn from two patients, A and B. A was suffering from syphilitic facial paralysis, and B from secondary syphilis without any cranial sign. In both cases the fluid

was drawn off in two portions. In the case of A the first portion appeared quite clear; in that of B it was obviously contaminated with blood. Both portions were submitted to the test in each case, and the results were as follows :—

Case A (facial paralysis). First portion (possibly contaminated with blood): change of colour commenced at dilution 1 in 10 and reached its maximum at 1 in 40 with complete decolourization and blue precipitate. At 1 in 160 the colour was lilac, but at 1 in 320 decolourization was again almost complete, and the second maximum was reached at 1 in 640. The second portion of fluid showed only one maximum (blue-red at 1 in 40 and nearly as blue at 1 in 80).

Case B. First portion (obviously contaminated with blood): maximum first reached at 1 in 320 (complete decolourization), with some return of colour at 1 in 2,560. Second portion showed no change in any of the tubes.

It seems from these results that in both cases the first portion was contaminated with blood serum. Though the reaction could be read in the test of each portion of fluid A, it is possible that in fluid B the admixture with blood might have interfered with the reading, and it is advisable always to test the second portion drawn off, however clear the first may appear.

In conducting this test it is necessary to ensure that all articles which come into contact with the test fluids should be scrupulously clean, being thoroughly washed with distilled water and then dried by heat.

It is too early yet to pronounce definitely on the clinical value of Lange's test. My own limited experience bears out Lange's claim for it, but, naturally, the fluids from a large number of other pathological conditions of the central nervous system must be examined before the test can be pronounced to be specific.

Apart from its immediate clinical interest it suggests

another line on which the problem of distinguishing syphilitic from other sera by an easier method than the Wassermann test may eventually be solved.

The Wassermann Test.—The test of the cerebro-spinal fluid for the Wassermann reaction is conducted on the same principle as in the original blood serum test. As the fluid contains no complement it is unnecessary, and in fact undesirable, to heat it.

The strength of the reaction is best estimated by using varying quantities of fluid with the amount of extract usually used in the serum test. Larger quantities of fluid must be used than is necessary when testing blood serum; e.g., following the procedure recommended in the description of the blood test 1 volume of 1 in 5, 1 in 3, 1 in 2, neat fluid, 2 volumes of neat, and even 5 volumes of neat fluid may respectively be incubated with the determined amount of extract and 3 M.H.D. of complement.

The strongest reactions are given by the fluids of general paralytics, and amongst these by those in the most advanced stages. The statistics for paralytics vary considerably with different authors, but many of these must be based on the older procedure of using comparatively small amounts of fluid. Candler and Mann in 109 cases where the diagnosis was confirmed by autopsy obtained a positive reaction in every case. These workers use 0·4 c.c. of fluid, the unit being 1 c.c. of sensitized cells. Morton, using Browning and Mackenzie's technique, in which twice this quantity is used, obtained 30 positives out of 30 cases.

In statistics published up to date the fluids of tabetics have given a positive reaction in about 50 per cent. of cases. Here, again, when larger quantities of fluid are used in the test a considerably higher percentage of positive reactions may be expected.

A positive Wassermann reaction with the cerebro-spinal

fluid indicates a syphilitic affection of the central nervous system. At one time it was considered a distinguishing point of parasyphilitic fluids that they gave a positive Wassermann reaction, while, as a rule, the fluid in other syphilitic diseases of the central nervous system did not. It has been found, however, that the distinction is one of degree only. Quite a large proportion of purely syphilitic cases give a positive reaction here when sufficient fluid is used, while in normal cases ten times as much fluid as it is customary to use of blood serum will not give a positive reaction.

The stronger the reaction, however, the more clearly the indication that the disease is parasyphilis, and if a fluid fails to give a positive reaction when used in a large amount it is extremely strong evidence against parasyphilis, particularly general paralysis.

Noguchi's Luetin Reaction.—From time to time workers have experimented to discover, if possible, a method of diagnosing syphilis in a manner analogous to the cutaneous tuberculin reaction of von Pirquet, but till quite recently with doubtful success. Neisser produced a papular formation by inoculating the skin of syphilitics with extract of congenital syphilitic liver. A similar reaction was sometimes produced with normal liver extract. Meirowsky, Tedeschi, and Nicolas Favre and Gautier obtained similar reactions with extracts of syphilitic liver or of syphiloma, but Ciuffo failed with an extract of the organs of a congenital syphilitic. The results obtained by all these workers were inconclusive, probably because they were working too indirectly with the *Sp. pallida.*

In 1910–11 Noguchi made many experiments on rabbits with his cultures of *Sp. pallida.* Having prepared them with a series of intravenous injections of cultivated *Sp. pallida,* a month after the last injection he inoculated them intradermically with the same antigen and found that all of them had become allergic, the sites of inoculation becoming inflamed and

sometimes pustular. Normal rabbits, on the other hand, did not react. Following on this he tried the emulsion of *Sp. pallida* culture on man, the emulsion being prepared from six strains of the micro-organism. The results showed that the reaction was strictly specific to syphilis, 250 persons who were normal or suffering from non-syphilitic diseases failing to react. This has been confirmed by Cohen, Robinson, and Kämmerer, who have published observations substantially in agreement with the following table, which shows Noguchi's results. Dr. Noguchi very kindly furnished me with a supply of luetin and, with one exception mentioned below, my results have so far confirmed those of the above workers. Thirty-one patients suffering from other diseases were also tested and none of them gave the reaction. It will be noticed from Table IV that the luetin reaction is most positive in those cases of syphilis in which the Wassermann reaction is very likely to be negative, well-treated patients and those in the later stages.

Preparation of Luetin.—A pure culture of *Sp. pallida* in ascitic agar is rubbed up to a thick paste in a sterile mortar. To the thick paste which results is added little by little enough of a culture of *Sp. pallida* in ascitic fluid to make a perfectly liquid emulsion. This is sterilized by heating at 60°C. for an hour in a water-bath, and 0·5 per cent. tricresol added. In exactly the same way is prepared a control fluid made by rubbing up sterile culture medium with liquid, heating and adding the preservative.

Method of Application.—With a sterile pipette enough of each of the two fluids for the day's tests is diluted with an equal part of sterile normal saline. Using a separate syringe armed with a very fine needle, 0·07 c.c. of the diluted luetin is injected into the cutis vera of one upper arm and a similar quantity of the control in the same way into the other arm.

The Reactions.—*Negative.*—After twenty-four hours at

TABLE IV (Noguchi).

Luetin Reaction in Various Syphilitic Conditions and in Controls.

	Primary Syphilis.		Secondary Syphilis.				Tertiary Syphilis.				Congenital Syphilis.				Cerebro-spinal Syphilis.		Latent Syphilis.		Controls.			
	Symptoms Present.		Symptoms Present.		Symptoms Absent.		Symptoms Present.		Symptoms Absent.		Under 1 Year.		Late Cases.		Symptoms Present.				Normal individuals		Non-Syphilitic Cases.	
Luetin reaction .	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—	+	—
No antisyphilitic treatment .	..	13	..	..	..	..	..	..	..	..	..	..	..	..	..	..	24	6	..	50	..	200
Slight mercurial treatment .	1	12	2	25	..	..	12	..	..	..	5	18	..	..	..	..	..	..	..	..	..	..
Regular mercurial treatment .	..	..	..	..	14	3	31	..	29	1	1	3	15	1	5	5	..	..	..	..	..	..
Salvarsan and mercurial treatment . . .	..	..	1	..	42	12	..	..	22	3	..	..	9	..	..	..	..	..	..	..	..	..
	1	25	3	25	56	15	43	0	51	4	6	21	24	1	5	5	24	6	0	50	0	200
	26		99				98				52				10		30		250			
	315																					

each site of inoculation a small erythematous spot appears which recedes in forty-eight hours. No induration is left, but a small brownish papule about 3 mm. across may occasionally persist for some days.

Positive.—Noguchi distinguishes three types :—

(*A*) Papular. A large raised and indurated papule from 5–10 mm. in diameter appears in twenty-four to forty-eight hours. The indurated papule may be surrounded by a red area ; the size and induration increase slowly for three or four days and then gradually subside. This reaction is given by secondary cases under regular treatment, and very young congenital syphilitics.

(*B*) Pustular form. Commences as a papule, but about the fourth day the surface becomes oedematous, and miliary vesicles may form. Within the next twenty-four hours a vesicle forms and this is succeeded by a pustule which soon ruptures, either spontaneously or on friction, and becomes covered with a crust. Soon after the rupture the induration subsides and practically no scar is left. This type of reaction occurs most frequently in tertiary and late hereditary syphilis.

(*C*) Torpid form. This is rare. The immediate results of the inoculation appear to be nil, but after ten days or even longer the pustular form develops. This was observed by Noguchi in one case of hereditary syphilis, one of primary and two of secondary, all being under mercurial treatment. I have seen this form in one healthy person and am inclined to attribute it to late septic infection of the damaged area of skin.

The site of the control inoculation almost always becomes quite normal in appearance at the end of forty-eight hours, or at most a slight yellow pigmentation, the remains of an ecchymosis, may persist. Robinson noted in three cases which gave a severe luetin reaction of the pustular type a similar though smaller reaction at the control site. Two of these

cases were tertiary and one was latent. In one of the cases I tested at Rochester Row an exactly similar result was obtained.

Though further investigation is necessary before the luetin reaction can be said to be strictly specific to syphilis, it will be seen from the table that a considerable amount of evidence has already accumulated in its favour. Since it is most often positive in the class of case which very frequently gives a negative Wassermann reaction, if its reliability becomes definitely established it will prove a valuable addition to our methods of diagnosis.

CHAPTER VI

SYPHILIS: COURSE OF THE DISEASE

The course and manifestations of syphilis vary very widely in different cases; hardly any disease, in fact, presents such different forms as syphilis may do. These variations probably depend on: (*a*) the quantity and virulence of the spirochetes inoculated, (*b*) the patient's own resisting power to the infection, and (*c*) the ingestion of antisyphilitic medicaments, either in the form of antisyphilitic treatment or as a remedy for some other complaint, e.g., a few doses of blue pill for a supposed sluggish condition of the liver.

For the purpose of a general review of syphilis, we may most conveniently divide it into Early and Late syphilis. Under Early syphilis we would group what was formerly spoken of as: (1) the incubation period; (2) primary syphilis; (3) secondary syphilis; (4) reminders. Late syphilis would include: (1) tertiary or gummatous syphilis, and (2) parasyphilis.

EARLY SYPHILIS

The main characteristics of early syphilis are: (1) the spirochetes are present in great numbers; (2) they can be detected in practically every lesion; (3) they tend to invade every structure of the body and produce changes in every tissue in which they locate themselves. The principal manifestations occur at the site of inoculation, in the lymphatic glands, the skin and mucous membranes. As the infection

is general so the manifestations are spread more or less generally over the whole body; they are therefore said to be symmetrical, a point on which much stress was formerly laid in making a diagnosis of secondary syphilis. As spirochetes are present in every lesion and also in the blood of the patient, his blood and secretions, but especially the exudation from any lesion of the mucous membrane, are highly infective, a point which must be borne in mind by the young surgeon when examining cases of early syphilis, more especially so if the infection has recently taken place.

The Incubation Period.—After infection by the *Spirochaeta pallida* has taken place there is no local reaction or other sign of infection for a period of from 14 to 42 days; most commonly about the twentieth to twenty-fifth day a small papule forms at the site of inoculation. If Ducrey's bacillus has been inoculated at the same time as the spirochete, a soft sore may appear shortly after inoculation.

Primary Syphilis.—The primary lesion or chancre usually becomes fully developed about the end of the fifth week, by which time the nearest lymphatic glands will also begin to show enlargement. The chancre, like all other manifestations of syphilis, may present a variety of appearances according to the anatomical structure of the part in which it happens to be situated. As has been pointed out in Chapter II, on the pathology of syphilis, all syphilitic affections are granulomata and consist of a small celled infiltration of the walls of the blood vessels, hence apart from the severity of the infection, the manifestations depend mainly on the vascularity of the part infected. If this fundamental fact is borne in mind many of the striking differences noted in different cases may be easily understood. Another point about most primary chancres is that if the surface of the sore be lightly scraped and the sore then squeezed, more serum than blood exudes, while a non-syphilitic sore, when similarly treated, bleeds freely.

PLATE III.—CHANCRE ON THE SKIN OF THE PENIS.

The syphilitic chancre may present any one of the following appearances :—

1. *The Hunterian Chancre.*—This is a smooth cartilaginous sore usually found on the glans penis or inner surface of the prepuce ; when in the latter situation and the foreskin is retracted the Hunterian chancre may be seen to turn over as a solid mass. The sore may be more or less ulcerated and covered with a sloughy yellow membrane ; this condition is due to the inoculation of pyogenic germs. The Hunterian chancre is usually single, but may be multiple.

2. *The Syphilitic Abrasion.*—This is a circular, superficial erosion, level with the surrounding surface. On careful inspection a definite pinkish margin can be seen (but not felt) ; its favourite sites are on the prepuce and glans penis.

3. *The Scaly Papule.*—This is a small red indurated papule of irregular shape, with an abraded fissured surface ; it may be multiple and its favourite site is at the end of the foreskin or around the meatus.

4. *The Granulating Sore.*—This is a rounded fleshy-looking sore with a moist surface and sharply defined, but only slightly raised margin and little or no induration. It is much less common than either of the other two and is most commonly found on the skin of the penis, scrotum, thigh, or abdomen.

5. *The Phagedenic Chancre.*—This is a large indurated sloughing sore with a free semi-purulent discharge. It is generally situated on the glans penis and frequently extends on to the inner surface of the prepuce. There is always a great deal of surrounding inflammation and oedema, and not uncommonly the foreskin cannot be retracted, but the indurated mass can be easily felt through the swollen foreskin. This condition is almost certainly due to the simultaneous inoculation of a diphtheroid and of a pyogenic micro-organism along with the spirochete.

6. *Urethral Chancre.*—This is rather an exceptional site for

the inoculation of syphilis, but it does sometimes occur and the possibility must be borne in mind. When present, an indurated swelling, surrounding the urethra within an inch or two of the meatus, can generally be detected on palpating the penis; the urethroscope would also show the presence of the sore.

In females the syphilitic chancre is often multiple; the character of the sore is much the same as in the male, but there is a greater tendency to mixed infection with pyogenic organisms. The commonest sites for infection are around the vulva, on the labia and on the os uteri; in the latter position they can only be detected with the aid of a speculum.

Extra-genital Chancres.—These vary very much in their appearance, according to the site of their inoculation, probably largely owing to the different degree of vascularity in different parts of the body, but also to a great extent owing to the simultaneous or subsequent inoculation of one or more varieties of pyogenic germs. There is no such thing as a typical extra-genital chancre; the conditions described below are the commoner forms met with, but any sluggish sore which fails to respond to the usual surgical treatment should be regarded with grave suspicion and examined for the presence of the *Spirochaeta pallida.*

A chancre situated on the skin of the body or limbs usually presents a bright red, slightly raised, granulating surface with sharply defined margins and little or no induration; the sore may be surrounded by an area of inflammation. On the skin of the fingers or face a chancre is generally of a dark red or brownish colour with a dry almost scab-like surface; in some cases the surface may become moist and ulcerated. It is surrounded by an oedematous and inflamed area and the sore is indurated and distinctly raised above the surrounding surface, while the nearest lymphatic glands soon become enlarged.

Plate IV.—Chancre on Lip.

A syphilitic infection about the finger-nails takes the form of a callous ulcer which exudes a thin seropurulent pus; there may be some induration and there is always an area of inflamed skin around it. The sore is very liable to be mistaken for a whitlow or for a local septic infection.

On the tongue and tonsils the syphilitic chancre presents a pale strawberry appearance and may easily be overlooked. If palpated considerable induration is found, with but little inflammation; the nearest glands are always enlarged.

In some cases in which infection has taken place on a sterile skin, as when a medical man accidentally wounds himself when operating on a patient suffering from syphilis, no local reaction, i.e. no chancre, may develop, although all the usual signs of constitutional syphilis may appear in 32 days (E. Lane, *Lancet*, June 15, 1912).

The further progress of the chancre depends to a great extent on whether any antisyphilitic treatment is employed or not. In untreated cases the chancre is fully developed about five weeks after the date of infection; it may persist for some weeks and even in some cases for months, after which it slowly disappears again. Under appropriate treatment the disappearance of the chancre is much hastened, although in some cases it may persist most obstinately, in spite of treatment.

While the chancre is becoming fully developed the spirochetes are spreading over the whole body and soon give rise to clinical manifestations, of which the following are the principal ones:—

Lymphatic Glands.—With the appearance of the chancre the lymphatic glands nearest to the sore begin to enlarge and shortly afterwards those of the whole body become similarly affected. When the infection is a pure syphilitic one the glands do not become greatly enlarged and they remain discrete, forming chains of nodules which feel like solid rubber

balls when palpated. The consistence of a lymphatic gland invaded by spirochetes is quite characteristic, and students should take every opportunity of making themselves familiar with the condition, as it can hardly be mistaken for anything else. It must of course be borne in mind that a double infection may have taken place and that a bubo may be present in a man suffering from early syphilis.

Constitutional Symptoms.—At this, the commencement of the so-called secondary, stage of the disease, a certain amount of constitutional disturbance may be produced. The patient may suffer from general malaise with headache, fever and anaemia ; there will also be in most cases a slight but progressive loss of weight.

The headache of early syphilis is not usually very acute, but rather of the dull continuous type ; this is now generally believed to be due to spirochetal infection of the meninges, hence this symptom may be an indication for caution when it is proposed to employ salvarsan in the treatment of the case.

The pyrexia is not usually severe, being of a mild continued type, the temperature showing a rise of 1° to 2° in the evening and a fall to normal or nearly so in the morning. The pyrexia soon ceases when appropriate treatment is begun, but in the absence of antisyphilitic treatment it may continue for some weeks and has even been mistaken for typhoid fever.

The anaemia is not as a rule marked in persons who are leading a healthy outdoor life ; when present it shows mostly as a pallor of the skin areas surrounding the mouth and eyes.

The loss of weight is generally from one-half to a couple of pounds a week, and is only detected when the patient is weighed at regular intervals.

Skin Eruptions.—About two months from the date of infection a rash usually appears, first on the chest and abdomen, but if not controlled by treatment it soon spreads over

Plate V.—Macular Syphilide.

PLATE VI.—PUSTULAR SYPHILIDE.

the whole surface of the body, being more marked on the flexor than on the extensor surfaces of the limbs.

The commoner forms of eruption are: (*a*) *the roseola* or *macular syphilide.*—This is usually the earliest rash of syphilis and appears on the lower part of the chest and upper part of the abdomen. It consists of small rounded or oval erythematous spots or patches, not raised and which disappear on pressure. Later they become dusky brown and may leave some staining. Under efficient treatment the roseola rapidly disappears.

(*b*) *The papular syphilide.*—This eruption occurs in two varieties, the small and the large papular syphilide. The papules have a great tendency to occur in groups. The colour is always much deeper and more pronounced than that of the roseola; the papules are distinctly raised, have a flat surface and when palpated feel firm. The eruption occurs on the body, also on the neck and forehead. After a short time the papules acquire a raw ham or so-called copper colour. In untreated cases the papules may disappear in time or they may become scaly, forming the papulo-squamous syphilide; if vesicles form on the papules the eruption is called a papulo-vesicular syphilide; suppuration may occur in the vesicles and give rise to a pustular syphilide, or should the vesicles dry up and form crusts the eruption is called a papulo-crustate syphilide.

(*c*) *The follicular syphilide* forms around the sebaceous follicles; it may be of the large or small variety. This eruption is not so common as the preceding varieties, it is of a more coppery colour and is very resistant to treatment; when the follicles become absorbed they usually leave pigmented spots, which persist for months.

(*d*) *The nodular syphilide.*—This is a later eruption of the secondary stage, and occurs in severe or badly treated cases. The nodules are large and rounded, or oval, are of a deep red

almost beetroot colour, and have a firm consistence. Blebs may form on the nodules (bullous syphilide), or suppuration may occur (ecthyma), or a crust may form and assume somewhat the shape of a limpet shell (rupia). With the improved methods of treatment now employed these severe forms of syphilitic eruption, which were formerly quite common, are rarely seen.

(*e*) *Leucoderma* occurs in the later stages of secondary syphilis. It occurs on the neck, in persons having a deeply pigmented skin, in the form of small pale almost white patches, surrounded by areas of pigmented skin; it may present a beautiful lace-like pattern, and when present is diagnostic of syphilis.

(*f*) *The squamous syphilide*, or so-called syphilitic psoriasis, occurs late in the secondary stage of syphilis, mostly on the palms of the hands and soles of the feet. The scales are somewhat scanty, of a dirty white colour, and do not present the heaped-up glistening white appearance of true psoriasis.

In persons who have been insufficiently treated syphilitic skin eruptions may take on almost any form and may imitate more or less any of the skin diseases, but generally fail to conform to some important feature of the true skin disease, i.e. syphilis tends to produce what may be called a "sport," to borrow a horticulturist's expression, and any such when found should be suspected of being syphilitic in nature.

(*g*) *Alopecia* is a fairly common manifestation of secondary syphilis. The whole of the hair of the head tends to become thin and to present an unhealthy appearance; small bald patches are formed, so that the scalp presents somewhat the appearance of a fur rug badly eaten by moths. The bald patches are much smaller than those of alopecia areata, are not so sharply defined and do not present the smooth pink surface so characteristic of the bald patches in alopecia areata.

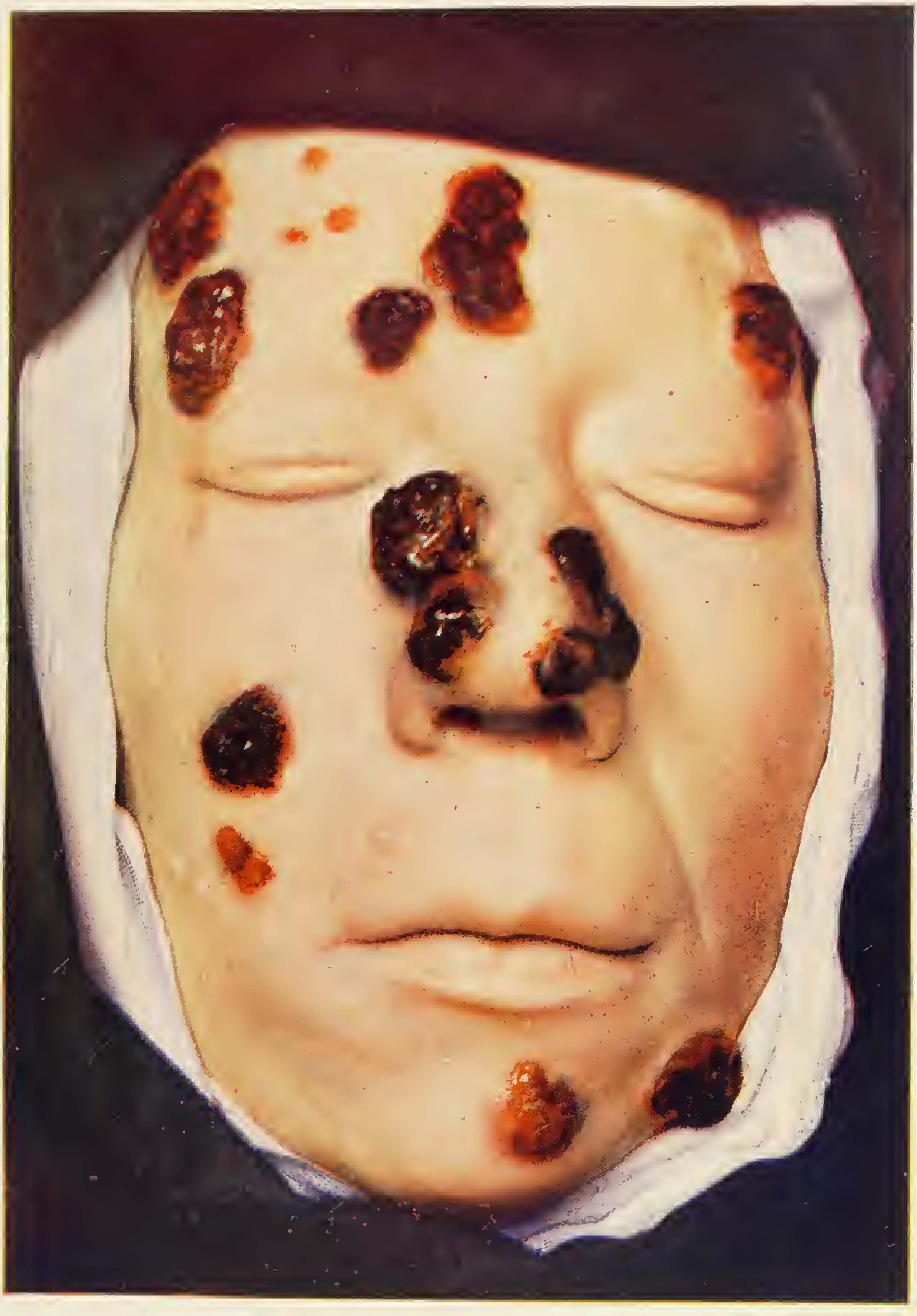

PLATE VII.—RUPIAL SYPHILIDE.

Plate VIII.—Leucoderma.

Mucous Membranes.—In early syphilis the palate may present a simple congestion. At a stage corresponding to the appearance of the papular syphilide mucous patches frequently occur. They may be situated anywhere on the mucous membrane, but are most commonly found near the tip of the tongue, inside the lips or on the fauces and tonsils. At first they have a pale, white look, as if a drop of diluted white enamel had been let fall on the membrane. The margin is always sharply differentiated from the surrounding tissue, and this serves to distinguish it from the dead white patch of hypertrophied epithelium resulting from the irritation of a sharp tooth. The patch may resolve under treatment, or become ulcerated in the centre, or especially in the tongue, heaping up of epithelium may take place leaving a solid looking whitish patch. On the dorsum of the tongue the epithelium may be greatly diminished, giving rise to a bald patch.

At the anus condylomata are not uncommon. These are masses of hypertrophied papillae having a pale pink to white colour and a moist surface. The sodden masses of dirty white epithelium seen in intertrigo must not be mistaken for condylomata.

CEREBRAL NERVES.

At this stage of the disease, i.e. about four to twelve months after infection, the peripheral nerves, but especially the cerebral nerves, are liable to be attacked by the spirochetes with consequent interference with their functions. This was not generally recognized till recently, when treatment by salvarsan was introduced; it then became the custom to examine patients, who had received this treatment, very carefully, to determine the effect, if any, on the nervous system. In a certain proportion of the cases it was

found that there was considerable interference with the functions of the cranial nerves, but especially of the auditory nerve. At first syphilologists were inclined to attribute the damage to the action of salvarsan, but on further investigation it was shown that lesions of the cranial nerves occurred in a certain proportion of persons suffering from syphilis, quite independent of the form of treatment adopted, and even more so before any treatment at all had been begun. Thus von Zeissl (*Berlin Klin. Wochenschrift*, No. 45, 1911) examined Schmidt's Jahrbücher from the year 1845 to 1904 and found records of more than 150 cases in which facial paralysis, deafness or retinitis had occurred within twelve months of the infection taking place. Benario (*Münch. Med. Wochenschrift*, No. 40, 1912) quoted a report by Fehr, in charge of the ophthalmic department of the Virchow Hospital, which states that 2,636 persons were examined for lesions of the eyes before receiving treatment by salvarsan. Among these, syphilitic changes in the eyes were found in 217 cases = 8·23 per cent. In 58 (=2·2 per cent.) of these persons the optic nerve showed early inflammation due to syphilis. A considerable number of cases of optic neuritis due to syphilis were also sent for treatment to the eye department from other departments of the hospital.

Iritis.—This usually attacks one eye at first, but the other may subsequently become affected. It is generally painful and a great deal of inflammatory lymph may be poured out, thus quickly causing adhesions to form between the lens and the iris, a point which must be remembered when treating this manifestation.

Orchitis.—Syphilitic orchitis may occur during the later secondary stage of syphilis. Usually only one side is attacked; the body of the testis is mainly affected and the swelling is usually painless or only slightly so; it may be accompanied by hydrocele.

Synovitis of the larger joints, especially of the knee-joint, is not uncommon.

A mild form of periostitis of the long bones may give rise to rheumatic pains.

Hemiplegia may occur suddenly or come on gradually; it is due to blocking of the cerebral arteries, the result of changes in the intima caused by the spirochetes.

LATE SYPHILIS

The expression "late," as used here, has no reference to the time which has elapsed since the infection took place—this may be months or years; the expression merely refers to the stage which the disease has reached.

When speaking of early syphilis it was pointed out that soon after infection the spirochetes invade every tissue of the body and that consequently the manifestations are generalized and the patient's blood and also the exudation from the lesions are highly infectious. In late syphilis, on the other hand, the spirochetes are scarce or at least can only rarely be detected in a lesion, and hence the lesions of late syphilis are only slightly infective.

Another important characteristic of late syphilis is that the spirochetes instead of spreading into every tissue of the body tend to locate themselves in one or more foci corresponding to which we find isolated lesions, i.e. gummata in place of the generalized lesions of early syphilis. In each case one structure or organ seems to be singled out for attack and each succeeding manifestation occurs in the same tissue or organ. Thus if a gumma of the skin is the first lesion, each relapse takes the form of a gumma of the skin, although of course when a gumma of the skin breaks down and becomes an ulcer the destructive process may attack the surrounding structures.

In venereal practice the commonest manifestations of late

syphilis are gummata and ulcers of the skin and subcutaneous tissue, tongue or palate, and periosteal nodes. The gumma presents itself as a firm rounded or irregular tumour, not infrequently ascribed to local injury, and believed by the patient to be merely a contusion. Owing to being non-vascular the gumma has a great tendency to undergo necrosis. In the process it first becomes soft, then fluid and resembles a chronic abscess, but if aspirated only a thin brownish glairy fluid is withdrawn. If the necrotic process is allowed to proceed the skin becomes thinned, then dusky brown in colour and finally breaks down, leaving a deep ulcer, with clean cut edges and a sloughy base, which discharges a thin seropurulent fluid. The ulcer tends to spread and destroy the neighbouring parts. In the periosteum the gummatous deposit forms a node most commonly seen on the shin-bone. A gumma may form in any tissue or organ and the symptoms naturally vary according to the organ or tissue attacked, and the mechanical pressure which it exerts on important parts, e.g. ducts or nerves.

Gumma of the meninges may give rise to the symptoms of cerebral tumour; one situated at the base of the brain may press on a cranial nerve and cause paralysis of the parts supplied. This is especially liable to happen in the case of the oculomotor nerves and so cause ophthalmoplegia.

A gumma is usually painless unless it happens to press on a nerve.

Parasyphilis.—Syphilis induces changes in the structure of the central nervous system and gives rise to a variety of diseases; the commonest of these are locomotor ataxia and general paralysis of the insane.

Syphilis also causes degenerative changes in the walls of arteries, which favours the formation of an aneurysm and in a similar way tends to produce incompetence of the aortic valves.

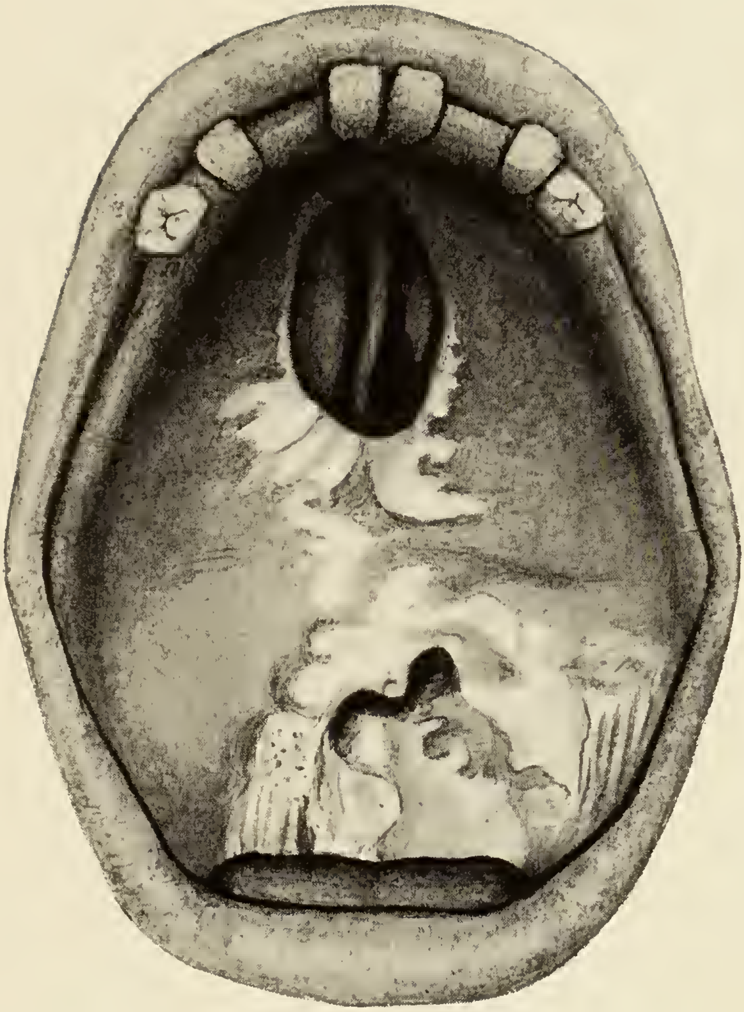

PLATE IX.—Tertiary Syphilis; destruction of palate.

[To face p. 146.

PLATE X.—CONGENITAL BULLOUS SYPHILIDE.

PLATE XI.—Congenital Syphilis; Hutchinson's teeth.

[To face p. 147.

Congenital Syphilis.—If the mother contracts syphilis while pregnant, abortion is extremely likely to occur or the child may be stillborn. Should the child be born alive, it may appear to be perfectly healthy, but in a month or so it develops coryza, commonly called "snuffles." Soon after a coppery papular, scaly, pustular or bulous rash appears on the skin and the child begins to waste and to look ill. Condylomata at the anus and on the scrotum in male children are commonly present when treatment is delayed. The epiphyses of long bones may become swollen and painful, the condition being usually attributed by the mother to some local injury.

Under treatment, except in some of the more severe cases, the child will usually rapidly improve in health and may appear to be quite well for some years. After a variable time one of the following manifestations may appear: interstitial keratitis, synovitis, periostitis or deafness. With the exception of the latter the trouble will generally more or less completely disappear under appropriate treatment. As a result of congenital syphilis the upper central incisors of the permanent teeth are usually contracted at their lower margin, which also shows a crescentic notch. This is quite distinct in character from the ridged and deficient enamel which occurs as the result of stomatitis and mercury during early infancy.

Diagnosis.—*General Remarks.*—The importance to the patient's future welfare of detecting syphilis at the earliest possible moment after infection has taken place, cannot be overestimated. Every day, one might almost say every hour, during which the spirochetes are allowed to multiply and invade fresh tissues, adds enormously to the gravity of the disease and to the chances of serious trouble occurring at some future date. When a patient presents himself with a possible syphilitic infection the surgeon must make use

of every means at his disposal to determine the true nature of the lesion. Thanks to the advances in our scientific knowledge of syphilis it is now not necessary to wait till the spirochetes have invaded every tissue of the body and produced profound changes in them, as shown by unmistakable manifestations of the disease, before forming our diagnosis. A few drops of serum expressed from the deeper layers of a suspected sore and subjected to microscopical examination will in most cases afford evidence of the presence or absence of spirochetes. At later stages of the disease when any doubt exists as to the diagnosis a sample of the patient's blood can be tested for its serum reaction. Even when a pathologist is not attached to the staff of the institution, the present postal facilities enable us to send specimens to a considerable distance and to receive a telegraphic report, in the course of a few days, which in most cases will settle the question of the diagnosis without a long period of waiting and the accompanying harm to the patient.

Clinical Diagnosis.—In the very early and late cases the surgeon is almost entirely dependent on the laboratory for his diagnosis ; still it must be remembered that the patient in the first place seeks the doctor's advice, and if the doctor is not familiar with the many forms in which syphilis may present itself, he may not appreciate the necessity for calling in the pathologist's help. In cases presenting well-marked signs of syphilis, the surgeon should be able to make up his mind without the pathologist's assistance, although he may like to have his diagnosis confirmed in the laboratory.

The intention of the above remarks is merely to remind the reader that, in spite of the enormous advantage to be obtained from the assistance of the pathologist, a study of the clinical aspects of syphilis should not be neglected.

EARLY SYPHILIS.

The chapter on the course of the disease really contains the essentials of clinical diagnosis; actual experience is, however, of the greatest importance, and no student should miss any opportunity of thoroughly examining every case of syphilis which he may happen to see.

When forming a diagnosis of syphilis from clinical evidence the surgeon must examine the patient thoroughly, and not be content merely to glance at the sore or any other manifestation which the patient may choose to show him; after having completed the examination, all the points for and against syphilis must be carefully weighed, remembering that the negative ones have little value, before committing himself to a definite diagnosis of syphilis. Very few of the manifestations are sufficiently characteristic of the disease to permit of a diagnosis being formed from a single one of them, except by an experienced surgeon. It is most important to remember that we cannot safely exclude syphilis because, at the time at which the lesion is seen, it does not happen to present the typical characters of syphilis.

Examination of the Patient.—When examining a patient for syphilis it is well to follow some routine plan. When this is done no symptom of importance can well be overlooked, and after a little practice the examination can be rapidly carried out. The plan sketched below is that followed in Professor Lang's clinic at Vienna and meets all requirements.

Begin by inquiring as to the dates of exposure to infection and of the appearance of the sore; occasionally definite answers are obtained, but, if, as so frequently happens, the replies are vague, proceed at once with the inspection, for which purpose the man must be stripped. Begin with the sore or sores, noting the number, position and characters. Next, using both hands simultaneously, one for each side

of the man's body, palpate the glands in both groins, the epitrochlear glands lying on the triceps tendon above the inner condyle and the sub-occipital and cervical glands. Note which of these are enlarged, and exclude those due to some cause other than syphilis. Now carefully inspect the whole surface of the body, beginning in front and finishing with the dorsal surface. Tell the man to stoop down, separate the buttocks and show the anus, on rising again he should hold up the soles of his feet.

Next place the man opposite a good light and tell him to protrude his tongue and move it slowly, so as to expose every part to view. Then using a glass tongue depressor to manipulate the parts, carefully examine the mucous membranes of the lips, gums and cheeks. Finally inspect the palate, fauces and tonsils; while doing so the surgeon must be prepared for an explosive cough with the expulsion of possibly infective mucus. Iritis should then be excluded, and finally, the scalp examined for specific alopecia.

In forming a diagnosis in the case of a person who is suspected of having recently contracted syphilis, we have to consider the following :—

(1) The history of the lesion.

(2) The appearance of the initial or other lesion.

(3) The condition of the lymphatic glands.

(4) The appearance of the skin.

(5) The mucous membranes.

The information derived from a consideration of the above points is our main guide in forming a diagnosis; some confirmatory evidence may be obtained by observing the body weight, from the existence of headache, anaemia, pyrexia and albuminuria.

(1) *The History of the Lesion.*—If we could always rely on the accuracy of the patient's statement it would afford us valuable help in forming our conclusions. Unfortunately

the patient is frequently uncertain as to the dates of exposure and of the appearance of the sore, or the exposure may have taken place on more than one occasion within the preceding month or so. The net result is that the history is rarely of much help to us.

(2) *The Initial Lesion.*—Some of the fluid expressed from the deeper layers of the sore would as a matter of course be submitted to microscopical examination for the presence of spirochetes, but before obtaining the specimen it is of the utmost importance to ascertain definitely that no form of antiseptic preparation has been employed locally; if any disinfectant has been applied to the sore it will be necessary to wait for at least a week before taking a specimen of the serum, as otherwise no spirochetes will be found even if the sore is a syphilitic one.

As to the appearance of the sore it must be remembered that this will vary considerably according to the time which has elapsed since the infection took place, and further that it may have undergone considerable modification in consequence of the application of some mercurial preparation. Should the sore present definitely syphilitic characters it is a strong point, in the case of a Hunterian chancre practically a decisive one, in favour of a positive diagnosis. On the other hand the patient may present himself with a typical soft sore, yet we cannot exclude syphilis, as a double infection may have taken place.

If the surgeon cannot give a definite diagnosis the patient must be told to present himself again, at intervals of about a week, till some further evidence is forthcoming, for a period of, say, three months; if no further signs have shown themselves by the end of this period we may pretty safely say that the patient is not suffering from syphilis.

The beginner must be somewhat chary of regarding every "indurated" sore as a syphilitic chancre. Induration is

certainly one of the main characteristics of syphilis, but it may be simulated by inflammatory oedema resulting from the application of irritant substances to a non-syphilitic sore. When examining a sore for induration it should be palpated with the forefinger alone, when a true syphilitic indurated sore feels like a piece of gristle; if the sore is pinched up between the forefinger and thumb it is much more difficult to distinguish between inflammatory oedema and syphilitic induration.

(3) *The Lymphatic Glands.*—As has already been stated, the lymphatic glands become enlarged about the time that the chancre is fully developed. The important point from a diagnostic point of view is that all the glands in the body are simultaneously affected and that they form chains of discrete firm tumours. The glands in the neck, groin and at the elbow are those which can be most readily examined.

(4) *Skin Eruptions.*—Syphilitic rashes are better seen when the skin is cold and when looked at from a short distance, say about a yard from the patient. In hot countries the early rashes may be quite atypical at first. The drug rashes must also be borne in mind, as the patient may have been treating himself for gonorrhoea with copaiba or some other drug, which may have produced a rash simulating a syphilitic one.

A few remarks may be made with reference to the mistakes which are likely to be made in diagnosing syphilides. The condition which the Germans call *Cutis marmorata* consists of a livid network of vessels enclosing healthy skin; this point distinguishes it from a macular syphilide. Pityriasis rosea has a delicate pink appearance and, if the original patch be looked for, a buff coloured centre with a fringe of fine scales is seen. Psoriasis, when occurring in small discrete patches, may easily be mistaken for a syphilide. If, however, a patch of psoriasis be gently scratched with the

finger nail quantities of fine silvery white scales come away, often in an adherent mass, leaving a deeply congested or even bleeding surface, and there is no induration at the site. A squamous syphilide, on the other hand, has dirty white scales in scanty quantities, the lesion is indurated and frequently situated on the flexor surfaces of the limbs. Lichen planus presents an angular marking, has a burnished metallic surface, and a distinctive violaceous colour.

(5) *Mucous Membranes.*—Mucous patches occur somewhat later than the first rashes of syphilis; in the absence of efficient treatment they may recur at intervals for several years. A typical mucous patch can hardly be mistaken for anything else and is diagnostic of syphilis.

The information derived from a consideration of the above points forms our main guide in coming to a conclusion as to the presence of syphilis or otherwise. As to the other signs, a slight but continuous loss of weight affords valuable confirmatory evidence, but if no loss of weight is taking place, especially in an otherwise healthy man, it does not help us to exclude syphilis. Pyrexia of a simple continued fever type, not due to other causes, points to syphilis, but in most cases the pyrexia is absent or is so slight as to escape notice. Headache and anaemia may occur in early syphilis, especially among men living an indoor sedentary life; but in robust persons leading a healthy outdoor existence these signs are rarely met with. Albuminuria is not a common sign of early syphilis; when it does occur the amount of albumen present is generally low and the arterial tension is not raised.

Late Syphilis.—In many cases the manifestation is a typical one and the diagnosis is easily made; in other cases the symptoms may be most indefinite and it may be impossible to state whether syphilis is present or not. It is in these cases that the pathologist can give invaluable assis-

tance by testing the patient's serum reaction. The syphilologist need not trouble to search for spirochetes, as it is most improbable that any will be found even in a well-marked lesion of late syphilis.

The manifestations of late syphilis usually seen by the syphilologist are gummata and ulcers of the skin and mucous membrane and periostitis.

A gumma if typical is easily recognized, but when the necrotic process is commencing and the mass of the gumma has become soft it may be mistaken for a chronic abscess. Sometimes the gummatous mass takes on a very irregular shape, and the patient lays stress on the fact that the swelling began to appear after some local injury ; in these circumstances the surgeon may not for the time think of syphilis as a possible cause of the trouble.

The syphilitic ulcer with its clean cut edges and sloughy base is usually easily recognized ; in the tongue it has been mistaken for an epitheliomatous ulcer, and cases have been recorded in which epithelioma has been grafted on to a syphilitic ulcer. Ulcers of the tongue should therefore be most carefully examined before stating a definite opinion as to their nature.

A more severe type of destructive ulcer was formerly commonly met with, but thanks to improved methods of treatment, is now rarely seen. The favourite sites were the hard and soft palate, the nose and the shins. All the tissues from the skin down to and including the bone were steadily destroyed, resulting in hideous deformities and in many cases in the death of the patient.

Syphilitic periostitis or nodes used to be commonly met with, but are now becoming much less frequent. The shins and skull, probably on account of their greater exposure to injury, are the sites most usually affected. The history of the swelling, its shape and extent, together with its firm

consistence and relative painlessness, are very characteristic, and the diagnosis is usually easily made.

In patients suffering from late syphilis, especially if they are hard smokers and spirit drinkers, the dorsum of the tongue often has a bald indurated appearance: the surface is deeply furrowed, the sides of the furrows are covered with a thickened white almost porcelain-like layer of epithelium, while the exposed surfaces are bare and bright red in colour.

Visceral Syphilis.—Gummata may form in any of the organs of the body, the liver being one of the favourite sites. The symptoms depend on the mechanical interference which the gumma produces on the functions of the organ. These cases usually find their way to the medical department of the hospital.

Central Nervous System.—A gumma may form in any part of the central nervous system, and by giving rise to pressure symptoms may be mistaken for a malignant tumour.

Syphilitic arteritis may occlude the vessels supplying important centres and so interfere with their functions, producing paralysis of the area controlled by that centre. General paralysis of the insane or locomotor ataxia may supervene as a sequel of syphilis. In all these conditions the physician is usually called on to form a diagnosis and the syphilologist is merely asked to carry out a serum test.

Doubtful Cases.—In every case when the manifestations are obscure a specimen of the exudate from the initial lesion, or in later cases a specimen of the patient's blood, should be submitted to laboratory examination by an experienced pathologist; even if there is no pathologist in the station, the postal facilities open to us should permit of this test being carried out and of an answer being received within a few days; this obviates the long waiting for confirmatory signs to appear, during which time the patient's tissues may suffer immediate damage. If it is impossible to obtain

assistance from the pathologist, especially in cases of late syphilis, the therapeutic test may then be resorted to. This consists in noting accurately the man's condition, the state of any lesions and his body weight. Then, bearing in mind the cautions to be observed before employing any form of energetic antisyphilitic treatment, select one of these, according to the patient's condition and the facilities for treatment; after, say, a fortnight's treatment, re-examine the patient and compare his condition with that before receiving the treatment. If a marked improvement, not merely a slight one which might be accounted for by a more careful mode of living, has taken place, the presence of syphilis may be pretty safely assumed and a regular course of treatment carried out. A mere statement by the patient that he feels better must not be accepted as evidence of the beneficial effect of mercury.

Table of Values in Diagnosis.—This table was drawn up before the discovery of the spirochete or of the serum reaction in syphilis; in consequence of these advances in our knowledge, it has lost most of its value as an aid to diagnosis. It has, however, been retained as a guide to beginners, to show the relative importance from a diagnostic point of view of the more important manifestations of syphilis.

Manifestation	Value
Hunterian chancre	9
Phagedenic chancre	5
Indurated sore (not the result of cauterization)	5
Relapsing sore (breaking down after having healed under non-mercurial treatment)	3
Granulating sore on the skin of the penis, which refuses to heal under non-mercurial treatment	5
Characteristic enlargement of groups of lymphatic glands, without other obvious cause	5
Roseolar or macular eruption (drug rashes excepted)	7
Eruptions not recognizable as belonging to any non-syphilitic class	2
Continuous slight loss of body weight not otherwise explicable	5
Anaemia, not otherwise explicable	2

Manifestation	Value
Pyrexia, of simple continued fever type, lasting 2–3 weeks, not otherwise explicable	2
Continuous headaches with exacerbations at night	2
Continuous malaise	2
Mucous patches (if characteristic)	8
Condylomata	8
Alopecia of the syphilitic type	5

CHAPTER VII

TREATMENT—GENERAL REMARKS

When the *Spirochaeta pallida* gains admission to the human system it produces much the same effect as does an invading army which lives on the country it has conquered, i.e. it flourishes at the expense of its host, and in doing so causes profound pathological changes in the tissues (see Chapter II). The longer the spirochete is permitted to multiply in the tissues the more serious is the damage which it inflicts on them. Hence it is of the utmost importance that the spirochete should be destroyed at the earliest possible moment by the employment of energetic antisyphilitic treatment as soon as its presence has been definitely recognized. On the other hand, it is a fatal mistake to begin treatment while there is any doubt as to the correctness of the diagnosis. If this is done it only leads to half-hearted measures, with the result that the manifestations are delayed and the patient, believing himself to be cured, drifts along till some late and possibly grave relapse sets in, when it is too late to arrest the degenerative changes which have taken place. If, therefore, any antisyphilitic treatment is begun, the surgeon must insist on the patient completing a full course of treatment unless the serum reaction, carried out at intervals for at least a year, continues to yield a negative reaction.

Another important point, which must be borne in mind when deciding on the form of treatment which it is proposed to adopt in any case, is that the prospect of curing the patient

depends largely on the efficiency of the initial course of treatment. If this is thorough there is, especially under modern methods, a reasonable prospect of effecting a complete cure. When the initial treatment is inefficient the serum reaction tends to remain positive for very long periods, in spite of the most energetic treatment employed at a later date. As long as the serum reaction remains positive the patient is a candidate for a relapse.

Drugs.—Up till 1910 our most efficient weapon against syphilis was mercury ; although its efficiency still holds good, we now have, thanks to Ehrlich's work, salvarsan and other organic compounds of arsenic which act much more rapidly than mercury. The administration of each of these medicaments will be considered separately.

SALVARSAN AND NEO-SALVARSAN

Arsenical preparations have been used empirically for many years in the treatment of syphilis, but prior to the introduction of atoxyl derived their value more from their tonic than any specific action.

In 1907 Uhlenhuth demonstrated the specific effect of atoxyl in fowl spirochetosis and, following on this, Hallopeau, Lambkin and others advocated its use in the treatment of syphilis. Atoxyl, however, though it often produced most marked clinical effects, had little or no influence on the Wassermann reaction, its effect was generally transient, and its use was occasionally followed by blindness.

Other preparations, notably arsacetin and atoxylate of mercury, were tried, but were found to have the same disadvantages as atoxyl, and organic preparations of arsenic were fast acquiring a bad reputation when Ehrlich introduced arseno-phenylglycin, which was quickly followed by dioxy-diamido-arsenobenzol or "592," an insoluble salt, the hydrochloride of which is the now famous "606," or salvarsan.

Ehrlich's discovery was not a chance find, but the result of a long systematic research with the object of finding a synthetic preparation which would, to put it briefly, destroy the parasites without at the same time damaging the tissues of the host.

Like its numerous predecessors, prepared and tested in Ehrlich's laboratory, it was synthesized by Bertheim and tested on animals by Hata, who found that it would destroy the spirochetes in fowl spirochetosis in a dose which was 1/58th of the amount required to kill the bird. Its curative action on rabbit syphilis, as well as its relatively low toxicity, was also found to be well marked, the lethal dose being 7 to 10 times greater than the curative. Alt was then asked to try the new preparation on man.

Alt's report, produced six months later, caused the greatest excitement throughout the world, and Ehrlich was inundated with applications for samples of "606." It was not, however, till it had been tried by selected observers in different parts of the world that, nine months later (December, 1910), it was placed on the market under the name of "salvarsan."

Probably no remedy has aroused such fierce discussion in so short a time as salvarsan. On the one hand, some of its more enthusiastic advocates, influenced by the almost magical immediate effects of the remedy on syphilitic lesions, the rapid disappearance of spirochetes from those lesions and the conversion of the Wassermann reaction to negative, announced after a few weeks' trial their belief that in "606" Ehrlich had realized his ideal, the "therapia sterilisans magna." On the other hand, detractors, recruited chiefly from those who had not tried "606," decried this departure from older well-tried remedies, predicted terrible things, and subsequently, ignoring all favourable reports, quoted from the literature all the accounts of deaths and other untoward

incidents which they could find to have followed the use of the remedy.

We may say now that if the early hopes have not been fully realized, neither have all the gloomy forebodings been justified, and salvarsan remains one of the great advances in therapeutics which is entitled to rank with quinine, chloroform and other blessings.

Description.—Salvarsan is a canary-yellow powder containing about 34 per cent. of arsenic. On exposure to air it becomes decomposed, forming a very poisonous compound, and for this reason it is put up in measured amounts in sealed capsules containing a neutral gas. For the same reason every capsule should always be carefully examined before use to see there are no flaws in the glass. In its present form it is readily soluble in water, in which it forms an acid solution. The addition of an alkali to this solution causes it first to become turbid and then clear, as the solution is first neutralized and then made alkaline. It is in this form that it is now most generally administered.

Technique of Administration.—Salvarsan may be administered subcutaneously, intramuscularly or intravenously. The two former methods were most popular at first, but have certain disadvantages which have led to their being largely abandoned in favour of the intravenous method. The chief of these disadvantages are the local pain at the site of the injection, which may be very severe; the risk of sloughing, especially after a subcutaneous injection; necrosis at the site of an intramuscular injection, and the slow, uncertain absorption of the remedy, with possibly some risk of arsenical poisoning from its decomposition. As an example of the slow absorption from the site of an intramuscular injection, Lieut.-Col. W. O. Beveridge, R.A.M.C., analysed one-third of an intragluteal nodule removed twelve months after an intramuscular injection and found in it 0·04 grm. of arsenic.

By intramuscular or subcutaneous injection it may be administered as an alkaline solution, a neutral suspension, or suspended in sterile olive or sesame oil.

The alkaline solution is prepared by rubbing up 0·5 grm. with 19 drops of a 15 per cent. solution of caustic soda, and then adding distilled water to make the total volume 5–10 c.c.

The **Neutral Suspension** is made by rubbing up 0·5 grm. in a sterile porcelain vessel with 8 drops of 15 per cent. caustic soda. The volume is then made up to 5 or 10 c.c. with distilled water, and tested to see that it is neutral. If acid, caustic soda is added; and if alkaline, dilute hydrochloric acid. The result is a fine flocculent suspension.

Suspensions in Oil are made by rubbing up the powder with the oil to make a 10 per cent. or weaker suspension.

The Injection is made with an all-glass syringe armed with a needle 2½ inches long and of fairly wide bore. For subcutaneous injection the best sites are between the scapulae and in the gluteal region. Whichever site is chosen the point of the needle must be in the subcutaneous tissue, and not in the cutis vera nor in the fascia overlying the muscles. The test of this is ability to move the needle about. The injection should be made slowly and the remedy distributed over as wide an area as possible by moving the point of the needle from time to time. After removing the needle the area should be well massaged so as to disperse the tumour.

For intramuscular injection the most usual site is into the gluteal muscles, the needle being entered at the junction of the anterior and middle thirds of a line joining the anterior superior iliac spine and the top of the gluteal fold. The needle is pushed in as far as it will go and at right angles to the surface. Before pressing the piston home it should be pulled on gently to make sure that the needle point is not inside a vessel. The injection must be made slowly and the needle removed quickly.

The immediate effect of a local injection is generally some pain which gives way in an hour or so to a feeling of soreness. On the following day, or the next, the pain frequently increases and may become so severe as to suggest that an abscess is forming. The temperature usually rises to about 101°, or may reach a higher point. These symptoms generally subside in five to seven days. Subsequently, after an interval varying from a fortnight to a few months, the skin over the site of a subcutaneous injection may slough, and the resulting ulcer may take many months to heal.

It is claimed by those who administer salvarsan suspended in oil that no pain follows. I have no personal experience of this method, but patients who have been treated with the oil suspension seem to have a vivid recollection of their discomfort afterwards.

For Intravenous Injection an alkaline solution is almost invariably employed. A few workers use a simple solution in distilled water, but this practice is not recommended.

Needless to say, all vessels and apparatus which come into contact with the solutions must be scrupulously sterile. Solutions must be freshly prepared with water distilled on the day of the injection. It is preferable to use a glass still and to reject the first 150 c.c. of the distillate. If a metal still is used the worm should be of pure tin and the first distillate should be rejected. The salt solution should be made only with pure sodium chloride.

The reason for using freshly distilled water and freshly prepared salt solution is that it has been found that febrile reaction is much more common after intravenous injections of salvarsan made with stale solutions. The cause of this is not quite clear. Wechselmann's explanation that it is due to the dead bodies of germs and their toxins which have accumulated in the solution between the time of its preparation and sterilization is the one generally accepted. Yakimoff and Kohl-

Yakimoff found that certain micro-organisms increased the toxicity of salvarsan very markedly. Hort and Penfold hold that an air-borne pyrogenetic substance which is heat-stable and will pass an ordinary filter gets into the water. The nature of this substance is unknown, but there are many facts which support Hort and Penfold's view. They believe that in the case of metal stills the pyrogenetic substance is aspirated into the still when the latter cools down. This may explain the fact that reactions are fewer when a glass still is used and when, in the case of automatic metal stills, the first half litre is rejected and precautions are taken to filter the air which is aspirated into the still as it cools.

The solution should not be in a greater concentration than 1 decigramme of salvarsan to every 30 c.c. Generally it is administered in a strength of 1 decigramme to every 40 to 50 c.c.

Instead of the directions supplied by the makers, the following method of making up the solution is employed at the Military Hospital, Rochester Row.

Assuming that 0·6 grm. is to be made up, into a glass vessel graduated to 300 c.c. is placed 100 c.c. of warm distilled water and the salvarsan gradually dissolved in it by stirring with a glass rod. When solution is complete, with no gelatinous particles remaining, 3·5 c.c. of a 4 per cent. caustic soda solution is run in and the mixture, which has become turbid, is stirred vigorously. The alkali is then added more slowly, while stirring, till a clear solution forms. As a rule this requires about 4·2 c.c. of the soda, and no more alkali should be added than is necessary for complete solution. The quantity in the glass vessel is then made up to 240 c.c. with warm 0·8 per cent. salt solution. The addition of the salt solution may cause a slight turbidity, which is dissipated by adding a drop or two of alkali. When ready the solution is set in warm water till the apparatus and patient have been finally arranged.

Many forms of apparatus have been devised for the intravenous injection of salvarsan. All of them are probably equally effective, but one on the principle of an ordinary infusion apparatus has the advantage of simplicity, and there is no breakable part of it which cannot be replaced in any hospital or at the nearest chemist's shop. The simplest form consists of a glass cylindrical funnel like the barrel of an ordinary glass syringe, to the nozzle of which is attached four feet of rubber tubing, which, in turn, is armed with a suitable needle. Two or three inspection windows in the form of short lengths of glass quill tubing are inserted in the course of the rubber tubing, the lowest being two or three inches from the needle end. It is a great convenience also to fit a strainer over the mouth of the funnel. A strainer devised by the writer has been found to work quite well (Fig. 11). It consists of two circular wire rings joined by two wire stays to make a short truncated cone. The wider ring fits outside and the narrower inside the mouth of the funnel. Ten layers of absorbent gauze are laid over the mouth of the funnel and the wire rings pressed into position, the narrower ring carrying part of the gauze before it (Fig. 12). When in position the funnel and strainer are sterilized together.

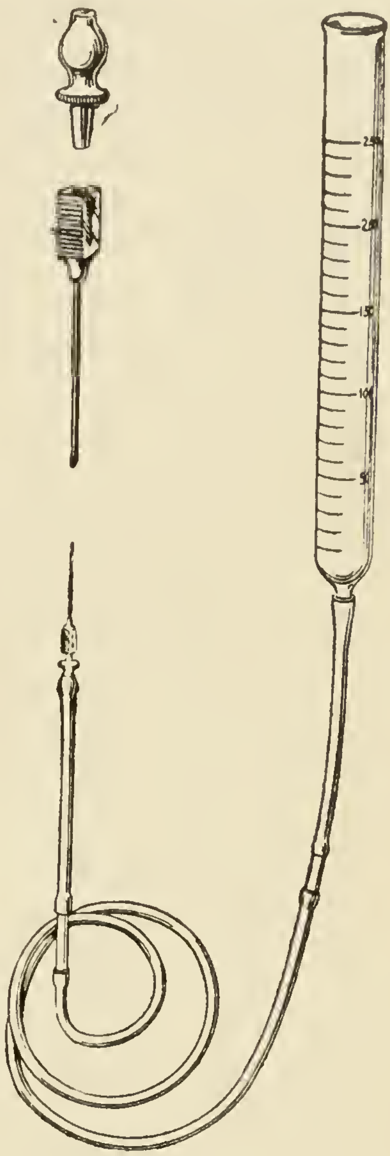

Fig. 10.

Fig. 11.

The funnel may be held in the hand or suspended from a

suitable stand. The needle should be a little wider than an ordinary hypodermic needle and its point shorter, so as to avoid any risk of damaging the other side of the vein during the injection. It is connected with the rubber tubing through a suitable metal piece. The needle known as Weintraud's serves admirably and is usually sold with the metal connexion. A clip is arranged on the rubber tubing about three inches from the needle end.

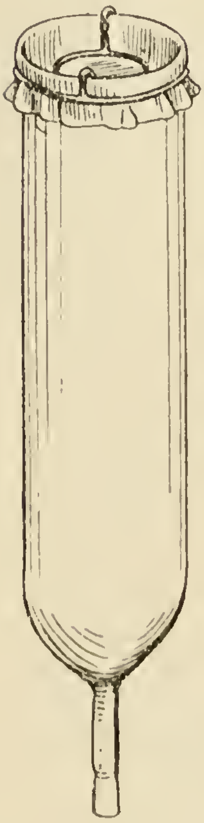

Fig. 12.

To use the apparatus the funnel is partly filled with salt solution (0·8 per cent.) with the clip occluding the tube. To remove air from the latter the funnel is lowered and the needle end of the rubber tubing held as high above the funnel as possible. The clip is then opened and the movement slowly reversed till salt solution begins to flow from the lower end. As it flows the needle is attached and the flow is stopped when the upper level of the salt solution stands about an inch from the bottom of the funnel.

The patient lies on the operating table, or in bed, and lays out his arm in a comfortable and convenient position. A rubber band is fastened round the upper arm so as to congest the veins on its distal side. To assist in this the patient should clench and unclench his fist a few times.

Over a prominent vein at the bend of the elbow the skin is painted with tincture of iodine, or a solution of iodine in chloroform (1 in 15). The funnel is then raised, and the operator, steadying the skin below the vein with a finger of the other hand, grasps the needle between finger and thumb and, holding it with its bevel uppermost and nearly parallel with the vein, pushes it steadily in. The rubber band is at once unfastened and the clip on the tubing opened.

A successful puncture is shown by—

(*a*) The operator's sense of touch.

(*b*) The steadily diminishing level of the salt solution in the funnel, with absence of any swelling over or round the vein.

(*c*) Possibly the appearance of blood at the window nearest the needle.

As the operator gains in experience, he will learn to rely on the signs in the order named and will then be least pleased to see blood at the glass window, since blood may clot in the tube and block the needle.

Before the salt solution has time to disappear down the tubing the assistant pours the dose of salvarsan solution into the funnel. When the upper level of the salvarsan has very nearly reached the bottom of the funnel more salt solution is poured into it and the solution is allowed to flow till the window nearest the needle has lost its yellow tint.

The salt solution which precedes the salvarsan acts as a pilot, since if the needle is not properly in the vein saline will not irritate the tissues. The salt solution which follows up the salvarsan solution clears the needle and the vein in its neighbourhood of salvarsan and prevents any chance of irritation in the needle track.

Difficulties.—In most men there is no difficulty if the vein is fairly firmly distended with blood and the skin is steadied. Very stout men who are also muscular may be troublesome subjects because the vein may not stand up at all and while the patient's fist is clenched it may not be possible to palpate the vein. In such cases it is sometimes an advantage to make the patient open his hand, and the vein can then be palpated. In some women there may be no signs of a vein at all, but one can generally be felt in the usual situation, and with a very careful deliberate puncture, keeping one's eye well on the area, there is usually no difficulty in entering the vein. When

the vein is very narrow, or cannot be felt, or the operator is afraid of missing his way, it is a good plan to detach the needle and search for the vein with it; when blood commences to flow freely from the needle the tubing is attached. The occasions when it is necessary to expose the vein by incision must be very rare, since in over 2,000 injections administered at Rochester Row, this has been done only once, and even in this case a subsequent injection was given without an incision.

After the solution has commenced to run into the vein it may stop or begin to run more slowly. One of three things has happened, and the cause must be investigated at once. (1) The eye of the needle is lying against the wall of the vein. If the needle is rotated or tilted the flow commences at once. (2) The needle has become dislodged and its point is lying in the tissues outside the vein. In this case a swelling forms over or round the vein. It may not be very obvious, since the solution may be flowing into the tissues on the deep side of the vein. The needle must be withdrawn at once, since salvarsan solution may cause very serious local disturbance, even sloughing of the subcutaneous tissues. (3) The needle is blocked with blood clot. In this case, also, the needle must be removed and cleared.

In hospitals and places where a stand can be arranged the form of apparatus shown in Fig. 13 will be found very convenient. It is merely the apparatus described above, with the addition of another funnel so as to have the main bulk of the salt solution in one funnel and the salvarsan in the other. It is extremely simple to work, and is especially useful when a series of cases has to be injected in a short time. The method of using it will be understood by referring to the figure. The left funnel is for salvarsan and the right for salt solution. With all the clips closed, salt solution is poured into the right funnel; to drive the air out of the connecting tubing, Clips 1

and 2 are opened to allow salt solution to flow, via the glass Y-piece, into the left funnel to a height of about half an inch from the bottom; Clip 2 is then closed and air is removed from the rest of the tubing by raising it, opening Clip 3 and then lowering till salt solution flows from the lower end of the tubing. Clip 3 is then closed, the salvarsan solution is poured into the left-hand funnel and all is ready. As soon as the vein has been punctured and the salt solution has commenced to flow satisfactorily, Clip 1 is closed and Clip 2 opened, leaving the way open for the salvarsan solution to flow down the tube. When the upper level of the salvarsan reaches the glass Y-piece, Clip 2 is closed and Clip 1 again opened to allow the salt solution to wash down the rest of the salvarsan in the tube and clear the needle. For the next case the last segment, Window D with the needle, is detached and replaced by a clean segment. At Window C a thermometer is shown in the illustration. It was introduced into the apparatus at Rochester Row in the hope that by keeping the temperature of the solution strictly at that of the body, the proportion of cases showing a febrile reaction following the injection would be reduced. It was found to make no difference, and since neo-salvarsan has to be given at room temperature the thermometer

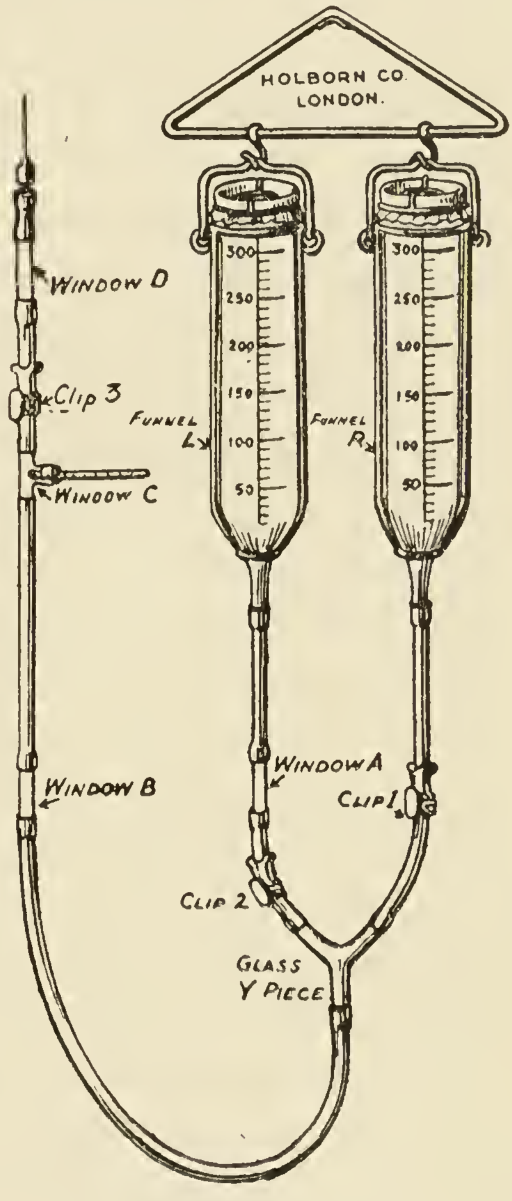

FIG. 13.

was discarded as an unnecessary complication. If the solution is luke-warm it is all right.

Immediate After-Effects of an Intravenous Injection.—Now that freshly distilled water is used and the salt solution is prepared on the day of the injection comparatively few patients suffer any inconvenience after an intravenous injection. In about one in five cases, however, there may be a rise of temperature (100·4° to 103·4°), and this may exceptionally be preceded by a rigor, with headache, vomiting and diarrhoea, which are very rarely severe. Generally all uncomfortable symptoms have disappeared by the following morning, but very occasionally there may be a rise of temperature on the evening of the following day. Sometimes the injection is followed by herpes and more rarely an erythematous rash or slight jaundice may occur.

About thirty cases have been recorded in which more serious symptoms have followed the injection. The symptoms of all these patients were very similar, and in nearly all of them followed the second of two injections administered within a week or less. Two to four days after the injection severe rigors with vomiting set in; these were followed by epileptiform convulsions and the patient died in coma about the fifth day; post-mortem examination showed punctiform haemorrhages in the brain and basal ganglia. In a case of this nature which came to the notice of the writer epileptiform convulsions commenced on the fourth day following the second of two intravenous injections of 0·6 grm. salvarsan given at an interval of two weeks. Death followed in twelve hours, and the most noticeable lesion found on post-mortem examination was hæmorrhage into the renal tubules, which were packed with blood cells. Capillary haemorrhages in the brain were not noted microscopically. The urine was normal beforehand and no febrile reaction followed either injection. Seven other patients injected on the same day suffered no reaction whatever.

The cause of these deaths has given rise to much discussion. Ehrlich believes they result from extensive liberation of spirochete endotoxins in the brain, since most of the cases of this nature have been in the early secondary stage, when we now know that there are often extensive meningeal changes. It would occupy too much space to discuss this question fully, and I can only say that I have found some difficulty in accepting this explanation. It is likely that most fatalities of this kind would be in secondary cases, since most patients treated with salvarsan are in this stage. Also if these untoward results are due to spirochete endotoxins it is difficult to understand why they did not follow the first injection, when, presumably, most endotoxins are released. In the case detailed above the cerebro-spinal fluid which was drawn off a few hours before death (and may easily have been slightly contaminated with blood) contained 20 cells per cmm. and gave negative Wassermann, Lange, Nonne and Noguchi reactions. It does not detract materially from the value of salvarsan to suggest that such symptoms as herpes, erythema, vomiting, diarrhoea and those which ended fatally as above are due to arsenical poisoning in exceptionally susceptible patients and that salvarsan has a cumulative action if it is repeated too early.

A few fatalities have occurred from pulmonary embolism after the injection. In some cases extensive thrombosis of the injected vein has occurred, and considerable irritation of the tissues at the bend of the elbow may follow if the solution has been allowed to flow into them instead of into the vein.

It is not necessary here to detail particulars of untoward incidents which have followed bad technique and the disregard of contra-indications. In illustration of the comparative safety of salvarsan I have been able to find accounts of only 200 deaths, and the number of injections must be over a million. Wechselmann reports no death due to salvarsan in more than 12,000 injections; Netter, one death (Queyrat's)

in over 6,500 ; at Rochester Row there has been no death in over 2,000 injections.

Much can be done to prevent unpleasant after-effects by using only freshly prepared solutions in the preparation of the salvarsan, by losing no time in administering it after opening the capsule and by proper preparation and after-treatment of the patient. The question of repeating the injection after too short an interval will be discussed later.

Preparation and After-Treatment of the Patient.—Previous to the injection the bowels should be well opened with a purgative and no food should be taken for four hours. After the injection the patient should go to bed and remain there till next morning. He should have no solid food for about four hours after, though a cup of tea may be allowed in two hours. If there is no vomiting or diarrhoea, a little soup and milk pudding may be taken in four to six hours. On the following morning he should rise late and lounge about all day, but ordinary meals may be taken if there is no other contra-indication. Violent exercise, over-indulgence in alcohol and similar indiscretions immediately after the injection may have been responsible for more than one calamity.

Therapeutic Effect.—Briefly, the immediate effect of a single injection of salvarsan is in most cases to cause a rapid disappearance of all outward signs of syphilis, and it is easy to understand the enthusiasm with which those who were the first to use salvarsan reported on it. They were accused of extravagance when they wrote of magical results, but the expresson does not appear so very extravagant to those who have seen, for example, mutilating lesions which were becoming steadily worse under most careful treatment with mercury and iodides commence to heal in twenty-four to forty-eight hours after a single injection of salvarsan ; or patients who previously could not swallow solids or even had to be fed by the nose because of the pain of syphilitic throat ulcers

Plate XII.—Extra-genital Chancre of Thumb, and Maculo-papular Eruption of Trunk. Taken immediately before an Intramuscular Injection of Salvarsan (0·6 grm.) at Military Hospital, Rochester Row.

Plate XIII.—Same Case ten days afterwards. Chancre almost healed; only stains of rash remain.

demand solid food within a few hours of the injection and swallow it with ease.

Its effect on *Sp. pallida* and the Wassermann reaction is not less striking and constitutes one of the main supports of its specific action. It is unusual to find spirochetes in such lesions as chancres and condylomata in which they abounded previously on the day after injecting salvarsan, and it is very rare indeed to find them on the second day, though no local antiseptic has been applied. In contrast with this, under mercurial treatment spirochetes can be found in sores, etc., ten days or more after the commencement of treatment, provided that no antiseptic is applied to the sore.

The Wassermann reaction varies in the length of time which elapses before it becomes negative. In cases which are negative when treatment commences, the reaction may occasionally be positive a week later, and then gradually become negative again. This is probably due to the same cause as the Jarisch-Herxheimer reaction discussed below. In cases which are positive before treatment the length of time which elapses before it becomes negative after a single injection seems to vary with the strength of the reaction. If very strong it may not disappear in a minority of cases, though even in these it generally becomes weaker. In others it takes from six to seven weeks, but in those who give a weaker reaction it usually disappears in about a month. In all cases where the reaction becomes negative it does so gradually, as though the Wassermann substance were being slowly excreted after the spirochete had ceased its activity.

The effect of salvarsan on parasyphilitic lesions is uncertain. In some cases of tabes it has caused the sexual power to return and the Argyll-Robertson pupil to disappear and has effected considerable improvement in co-ordination; in others it has proved disappointing and has sometimes even aggravated the symptoms. In most cases of general paralysis

it has proved disappointing. Most of the impressions regarding the effect of salvarsan on parasyphilis have been gathered, however, from results obtained when not so much was known regarding the best methods of giving the remedy, and better results are now being reported under improved methods.

Sometimes the immediate effect of salvarsan is to cause a temporary aggravation of the symptoms. Such a preliminary aggravation of symptoms, especially an increase in the intensity of the rash, was well-known under mercurial treatment as the Jarisch-Herxheimer reaction. After salvarsan it may appear in a few hours and generally disappears early on the following day. The temporary increase in strength of the Wassermann reaction has been mentioned and is probably due to the same cause. The Jarisch-Herxheimer reaction is generally attributed to a sudden flooding of the tissues with endotoxins of dead spirochetes, but may, conceivably, be due to their temporary increased activity, either immediately before death or under the irritating effect of a smaller dose than is sufficient to kill them. The Jarisch-Herxheimer reaction is important, since in certain situations, as in the brain, it may prove dangerous, or even fatal. Under other circumstances it may be useful in testing for the presence of syphilis in a patient who gives a negative Wassermann reaction. A small dose of salvarsan may provoke a positive Wassermann reaction if spirochetes are still present.

Apart from its specific action, salvarsan is an excellent tonic ; the patient's appetite often increases enormously ; it is quite common to find his weight go up as much as 20 lb. in as many days, and the feeling of well-being is quite a marked feature of salvarsan cases.

These are generally the immediate therapeutic effects of a single dose of salvarsan. Very occasionally, as far as we can judge at present, they may prove permanent, but in the great majority of cases, if reliance is placed on a single dose, a

relapse follows, and this is especially the case with regard to the Wassermann reaction. Patients who relapse remain free from symptoms for a varying time; after intramuscular or subcutaneous injection the time is, on the whole, longer, and this is probably because the remedy is more slowly absorbed into the circulation and keeps the spirochetes suppressed for a longer time. After a single intravenous injection the relapse of Wassermann reaction, with or without clinical symptoms, generally occurs in from six to twelve weeks.

The practical importance of this is that the surgeon should not be misled by the immediate effects of a single administration of salvarsan, however astonishing these may be, into believing that a cure has been effected. Much harm has been done by this; patients have been sent away under the belief that they were cured after a single dose. Many of them have been in a stage of syphilis, the late primary or early secondary, when we now know it is important that the attack on the spirochetes should be determined and prolonged if we are to avoid the risk of meningeal complications. In discussing the cerebro-spinal changes in syphilis the high percentage of cases in which lumbar puncture reveals pathological changes has been mentioned; it is evident that just as a generalized skin rash is peculiar to the early stages of syphilis, so are general meningeal changes, and it is particularly important that no risk should be taken of allowing the spirochetes headway at this time. This will be referred to in more detail when discussing "neuro-recidives" after salvarsan.

The Causation of Relapses.—It is difficult to explain why all the spirochetes in a syphilitic patient are not destroyed by a single injection of salvarsan. It is obvious that the specific effect of a single dose must be very profound, since spirochetes disappear so promptly from local lesions, and the Wassermann reaction changes so quickly to negative. As the explanation affects the question of dosage regulation,

its repetition and the use of such adjuvants as mercurial treatment, as well as the local treatment of sores, the possible explanations may be mentioned here. These are—

(1) That some spirochetes are resistant to salvarsan, and their descendants produce the relapse. Against this is the fact that relapses respond as promptly to a repetition of the treatment as in the first instance.

(2) That some spirochetes rapidly assume (or are in) a resistant form when the salvarsan is administered. Balfour has seen *Sp. pallida* extruding granules, especially after an injection of salvarsan, and believes that the granules are spore forms which are resistant to the remedy.

(3) That in syphilitic lesions some spirochetes are locked up in thrombosed vessels and within sclerosed areas where they are inaccessible to substances in the circulation. Subsequently when the processes of repair have opened out these sclerosed areas, long after the dose of salvarsan has been excreted, the surviving spirochetes escape into the tissues and reinfect the patient. In favour of this is the large proportion of primary case relapses in which the sore returns.

Whichever of the two latter explanations is true, it is evident that we can only expect to cure the patient by a process of intermittent sterilization. The details of this will be discussed later.

Closely connected with the subject of relapses is that of cranial nerve disturbances after salvarsan injections, the well-known "neuro-recidives," which have aroused considerable discussion. Briefly, in a certain proportion of cases—0·8 per cent. of 18,000 cases whose histories were collected from the literature by Benario—some disturbance of one or more cranial nerves has followed an injection of salvarsan. The symptoms have generally commenced from six to sixteen

weeks after the injection and have naturally varied with the particular nerve affected. Probably in the majority of cases it has been the auditory nerve, producing tinnitus, giddiness and deafness. In others the optic, facial, third, fourth, sixth or fifth nerves, or a group of these, has been affected. Sometimes the disturbance has been transient, at others it has gone on to complete paralysis of the nerve or nerves affected.

Organic preparations of arsenic have had an evil reputation for some time, and it needed only this to start the idea that salvarsan had a neurotropic effect. Finger, one of the foremost opponents of salvarsan, stated his belief that these nerve disturbances were directly due to salvarsan poisoning, and this opinion was supported by some others, including Gaucher. Driven from this position by the answer that salvarsan has been extensively used in the treatment of other diseases, but that in none of these have nerve disturbances followed, Finger then held that salvarsan by its damaging effect on cranial vessels produced a lowered resistance to the spirochetes in the cranial nerves. The answer to this was the fact that in animals salvarsan does not damage the vessels. Ehrlich has held from the first the belief that these cranial nerve disturbances are syphilitic relapses, and his views are backed by the overwhelming evidence which has been brought forward by Benario, Dreyfus and others, who agree that they manifest a local syphilitic meningitis. It would occupy too much space to detail all this evidence, but the following points may be mentioned :—

(1) Cranial nerve disturbances generally occur when practically all the salvarsan must have been excreted. (2) Similar lesions occur in syphilis apart from salvarsan, generally at the period, the early secondary stage, when the salvarsan cases have suffered from them. Hjelmann (quoted by Benario) states that 1·2 to 1·5 per cent. of all syphilitics develop some cranial disease, and Mauriac puts the proportion

much higher. Naunyn holds that in the vast majority of all cases of syphilitic brain disease the affection commences within a year from the primary sore. (3) The changes in the cerebro-spinal fluid—increase of lymphocytes, Nonne's and Lange's reaction, etc.—are exactly similar in neuro-recidive cases to those which are so frequently found in the early stages of syphilis. (4) Most of the cases have happened after the injection of a dose which we now know is quite insufficient. As an example of this Captain A. T. Frost, R.A.M.C., reported six cases in his first hundred treated with salvarsan. Five of them had received an initial injection which did not exceed 0·4 grm. and no other treatment. The sixth had two doses of 0·3 grm. at twelve days' interval. In contrast with this, at the Military Hospital, Rochester Row, where similar subjects were treated, but the treatment has been much more intense, out of 755 patients treated with salvarsan, only one instance of cranial nerve disturbance has followed. This was in a patient who received two injections of neo-salvarsan and no other treatment. His cerebro-spinal fluid gave Lange's reaction and contained 30 lymphocytes per c.mm. He was treated with more salvarsan in conjunction with mercury, and improved. The only other complications affecting the central nervous system which have so far occurred amongst the Rochester Row cases are one of spinal meningitis and one of hemiparesis. The former improved and the latter completely cleared up under energetic antisyphilitic treatment.

(5) The injection of more salvarsan, if administered before irretrievable damage has been done to the nerve, generally results in disappearance of the neuro-recidive. Captain Frost's evidence on this point is very valuable; he treated five of his six cases with more salvarsan and in all of them the symptoms disappeared. Amongst others, Gennerich and Dreyfus both insist strongly on the prompt use of salvarsan when cranial nerve disturbance commences. This in itself

appears to be a complete answer to those who assert that salvarsan has a neurotropic action.

It is stated, nevertheless, that these nerve disturbances have become more frequent since salvarsan treatment was introduced. It must be remembered that nobody ever thought of attributing to mercury any such complications. They occurred occasionally in the course of every-day practice, were looked on as manifestations of syphilis, and were generally not thought worth publishing. Further, many cases in the early stages of syphilis have been treated with a single dose of salvarsan and sent away in the belief that they were cured. If they were not cured, as we now know the great majority of them could not have been, they were in just the stage of syphilis when it is most important to keep the spirochetes under control for fear of damage to the meninges. Under mercury the treatment would have been prolonged, at any rate throughout the greater part of this period, and there is no doubt that if these complications were less frequent under mercurial treatment (it is impossible to obtain exact figures which show their relative frequency under each therapy), it was because under mercury the spirochetes were more or less continuously held in check throughout this critical period. Now that it is generally recognized that salvarsan treatment must be prolonged over some weeks, and especially under the combined treatment with salvarsan and mercury which has been found the best, we may confidently anticipate that there will be a great reduction, if not a total abolition, of these nerve complications.

It is necessary to dispose of this "bogey," the so-called "neurotropic action" of salvarsan, since it is capable of much mischief. I have seen irreparable damage follow in a case of fifth nerve paralysis which was not promptly and energetically treated with antisyphilitic measures, because, having occurred four months after an injection of salvarsan

(without any other treatment), it was attributed to salvarsan poisoning. In this case the cerebro-spinal fluid gave a positive Wassermann and Lange's gold reaction, and contained 150 lymphocytes per c.mm. Clearly a case of syphilis of the central nervous system. Some improvement had followed a few calomel and salvarsan injections at the time of writing, a few weeks after receipt of the case.

Choice of Cases for Treatment with Salvarsan.—*Relative Contraindications.*—In the beginning certain diseases were laid down as absolutely contraindicating the use of salvarsan. Experience has shown, however, that with careful regulation of the dosage it is possible to treat with salvarsan many patients suffering from these complications, and contraindications are becoming gradually less and less absolute. Salvarsan should not be given or only with the greatest caution, commencing with extremely small doses, to patients with extensive visceral lesions (especially if due to diseases other than syphilis), arterio-sclerosis, aneurysm, haemophilia, diabetes, or advanced disease of the central nervous system, including well-marked tabes and general paralysis.

Caution should be exercised when there is marked debility, in visceral disease of a milder type, in syphilitic disease of the central nervous system (including early cases of syphilis with well-marked headache), in early tabes and general paralysis, and when there is extensive congenital syphilis.

Indications.—With the above cautions salvarsan is indicated in all cases of syphilis, to which it may be administered in full doses, and we should by no means limit its use to cases where mercury has failed to arrest the disease or cannot be tolerated. Pregnancy is not a contraindication and it has frequently been given here in full doses for women with excellent results to mother and child. It would probably be safer, however, to treat such cases with divided

doses, combined with mercurial treatment, on a more continuous plan than to trust to one or two doses of salvarsan alone.

The safety of salvarsan in eye diseases has aroused some discussion chiefly on account of the eye complications which sometimes followed atoxyl. The relation of salvarsan to optic neuritis has been discussed under neuro-recidives and it need only be said here that Ehrlich has not been able to find proof of a single case of blindness due to salvarsan. At the same time it must be stated that optic neuritis should lead one to apprehend the presence of meningeal changes and on this account the treatment should proceed with caution. Syphilitic iritis may be treated with full doses of salvarsan, and the earlier the better, so as to avoid irreparable damage from syphilitic changes.

Suggested Schemes for the Treatment of Syphilis with Salvarsan.—Salvarsan was introduced so recently and so much time must elapse before the value of any particular line of treatment can be ascertained as regards its permanency, that there is very little unanimity amongst different workers as to the particular scheme which effects the largest proportion of cures. Consequently, only general principles can be indicated. The reader will not go far wrong, however, if he proceeds on the principle that there is no scheme which will guarantee 100 per cent. of cures, and that patients treated with salvarsan must invariably be watched afterwards both clinically and serologically as carefully as if they had been under exclusively mercurial treatment.

A few workers would still trust entirely to salvarsan, either in a series of full doses or in divided doses at closer intervals, but the majority, including Ehrlich, Neisser, Gennerich and many others, who perhaps have had a better opportunity of following up their cases, now strongly advocate that salvarsan should be used in conjunction with mercury, and this is the

practice which has been found the most successful at Rochester Row.

It has been the practice in many cliniques to inject large doses of salvarsan at comparatively short intervals, a week or less. This has proved quite safe in an enormous number of cases, but, as far as can be judged from the literature, those deaths which followed an injection of salvarsan by four or five days and were immediately preceded by epileptiform convulsions, etc., occurred for the most part in cases which had received two or more full doses at intervals of a week or less. Lieut.-Col. W. O. Beveridge, who examined the urine of a large number of patients treated at Rochester Row, found that after intravenous injection of a full dose of salvarsan arsenic could be found in the urine up to the eighth day, and this agrees with the results of other workers. The total quantity of arsenic found did not by any means correspond to the dose of salvarsan, and though a certain amount must have been excreted by intestines and skin, it is very possible that for some time a certain amount of arsenic remains locked up in the body. This is supported by the experiments of Stümpke and Siegfried, who found that in rabbits which were injected with salvarsan the bulk of the remedy was quickly taken up by the liver, smaller amounts being retained by other viscera. Though the quantity of arsenic in the viscera steadily diminished, traces of arsenic could be found in them for months. It is possible, therefore, that if given in full doses at too-short intervals salvarsan can exercise a cumulative action which may be dangerous to susceptible subjects. At Rochester Row full doses have not been administered at shorter intervals than two weeks, and this may account for the immunity from accidents which has been enjoyed there. At the present time, also, more and more writers are advocating a longer interval between full doses of salvarsan.

All workers are agreed on the great advantage of commencing treatment with salvarsan in the early primary stage; if possible, before the Wassermann reaction has become positive.

In illustration of the practice of different workers the following may be described.

Gennerich recommends six or more injections of salvarsan in conjunction with injections of calomel. The first two salvarsan injections are given at an interval of four days; the third, four to six days later; the fourth, six days; the fifth, seven to eight days later; and the sixth and subsequent injections at longer intervals, ten to fourteen days. In the course of about three weeks he would give eight small calomel injections ($\frac{1}{5}$ to $\frac{1}{2}$ grain). The nearer the patient is to the secondary stage (and in the secondary stage itself), the more prolonged the treatment must be. If a larger dose of 0·5 grm. salvarsan is given he recommends a longer pause between injections, not less than eight days.

Emery (France) gives in the primary stage six weekly injections of 0·3 grm., and after two months a second series of three weekly injections. In the secondary stage, five injections of 0·5 grm. at intervals of eight days and a second similar series at the end of two months, the period when relapses may be expected.

Scholz gives 0·6 to 0·8 grm. salvarsan at intervals of three to five weeks with an energetic mercurial course lasting five to six weeks.

At the Military Hospital, Rochester Row, different series of cases have been treated according to the following schemes, and their progress then watched from the clinical and serological points of view; (1) A single intramuscular injection. (2) Two intravenous injections of 0·6 grm. to men or 0·5 grm. to women who were otherwise healthy, at a fortnight's interval. (3) An initial intravenous injection of 0·6 grm.,

followed at intervals of two weeks by three intravenous injections of 0·2 to 0·3 grm. (4) An intravenous injection of 0·6 grm., nine weekly intramuscular injections of mercurial cream (Hg grain i in each), commencing two days after the salvarsan injection, and, lastly, an intravenous injection of salvarsan (0·6 grm.). (5) An intravenous injection of 0·6 grm. salvarsan, then two weekly intramuscular injections of calomel cream (Hg_2Cl_2 grain $\frac{3}{4}$ in each), an intravenous injection of 0·6 grm. salvarsan two weeks after the first, two more injections of calomel, and, lastly, an intravenous injection of salvarsan, 0·6 grm.

Our experience agrees with that of many other workers that the best results have been given by the series in which mercurial injections were administered in conjunction with salvarsan. Of the two combined series the better results followed that in which nine mercurial cream injections were given, and it is possible that this was because the treatment was more prolonged.

With this course more treatment is required for cases showing a positive Wassermann reaction or, to a much less extent, for clinical relapses in about 20 per cent. of secondary and 9 per cent. of primary cases observed for eight to twelve months, and it is possible that three salvarsan with nine mercurial injections would give better results. My own inclination is towards giving two or three full doses of salvarsan at intervals spaced out over nine or ten weeks, with energetic mercurial treatment in the intervals, rather than numerous small doses of salvarsan at short intervals in a course of shorter duration.

In primary cases it is very advisable to treat the sore locally, since spirochetes may here be locked up and inaccessible to the salvarsan. At Rochester Row the sore is excised, ionized with mercury, cauterized or treated with 30 per cent. calomel ointment in order of preference.

None of these require special mention, except ionization, which was adopted at Major C. E. Pollock's suggestion. A pad soaked in perchloride of mercury (1 in 1,000) is applied to the sore and to it is applied a button electrode connected to the positive pole of a constant current battery. To another part of the body is applied a pad of several layers of lint soaked in 1 per cent. sodium chloride, and in this is incorporated an electrode connected to the negative pole. The current is turned on gradually and as much allowed to pass for ten minutes as the patient can stand without marked discomfort.

Treatment when Caution is Necessary.—When there are indications that the central nervous system is involved, e.g., in meningitis, cranial nerve disturbance, thrombosis of cerebral vessels, cerebral gummata and in early tabes and general paralysis, it may be very dangerous to commence with full doses of salvarsan, and Ehrlich, as well as Dreyfus, would include in this caution all early cases of syphilis after the disease has become generalized; when, in fact, the Wassermann reaction has become positive, unless it is proved by a preliminary lumbar puncture that the cerebro-spinal fluid is normal. Ehrlich fears that in such cases full doses may produce severe intracranial reaction from release of spirochete endotoxins. Unless there is very severe headache, with perhaps some stiffness of the neck, and Kernig's sign is present, I would not hesitate to treat secondary cases with full doses on the plan already described.

Though caution is necessary in cases of meningitis and of cranial nerve diseases, this only applies to the commencement of the course of treatment. Later, when improvement has become well marked, the treatment may be bolder, and in fact it is particularly necessary that the course should be thorough.

The following plan of treatment is suggested for these cases.

Commence with two injections of calomel cream (Hg_2Cl_2, gr. $\frac{3}{4}$ in each) at three days' interval and after one more day commence salvarsan, giving 0·2, 0·2 and then 0·3 at intervals of two days, if each injection is not followed by marked disturbance. After a week's interval, 0·3 to 0·4 grm. salvarsan is given; after two weeks further 0·5 grm., and this is repeated twice at further intervals of two weeks. Between the injections of salvarsan weekly injections of calomel are given. This plan must be subject to modification, according to the progress of the case. It is certainly not quite so intensive as that recommended by Dreyfus, for instance, but does not run the risk of poisoning a susceptible case with salvarsan. The chief point to remember is that no time should be lost in commencing treatment, and this should be prolonged and thorough. It would be best, though probably not always practicable, to carry out the necessary tests, to continue treatment till the cerebro-spinal fluid no longer showed pathological changes. In any case the Wassermann reaction should be completely negative before treatment is suspended, and subsequent observation should be at short intervals.

In tabes Dreyfus recommends that a total of 5·4 grm. in doses of 0·3 to 0·4 grm. salvarsan be given in six weeks, with twelve injections of calomel or mercurial cream.

It has been found dangerous to inject infants suffering from severe congenital syphilis with salvarsan. It is believed that the child is overwhelmed with endotoxins of dead spirochetes. A better plan if the mother can nurse the infant is to administer the salvarsan to her. After a time when the child has improved considerably the treatment can be finished off with direct injections of salvarsan in doses of 0·002 to 0·005 grm. per kilogramme weight, and treatment continued in combination with mercury, as in the case of adults.

Observation of Patients after the First Course of Treatment.—It is difficult to give precise directions regard-

ing the frequency with which the patient should be examined subsequent to completion of a combined course of salvarsan and mercury such as that outlined above. The following routine which is carried out at Rochester Row was instituted after observing the behaviour with regard to relapses of a large number of cases.

At the end of the course the blood is examined by the Wassermann test and if found to be negative, as in the vast majority of cases, attendance is excused for twelve weeks. At the end of this time the blood is re-examined and every three months during the first year of observation. After the first attendance (three months from the end of the course) the patient attends for a clinical examination every four weeks for six months and subsequently every three months to the end of the period of observation. During the second year the practice varies with the stage of the disease at which the patient was first treated. If primary, the blood is examined twice only at intervals of twelve weeks from the last examination. If still negative (fifty-nine weeks from the commencement of treatment), he is excused further attendance. In secondary cases the patient continues to attend every three months and his blood is examined, once twelve weeks from the last test of the first year, and twice afterwards at six-monthly intervals.

If at any time the Wassermann reaction is found to be positive, treatment is at once recommenced. The same naturally applies to any return of clinical signs.

If at any time a patient gives a doubtful reaction his blood serum is tested again after a month. Frequently, either then or at the end of the month, a small dose of salvarsan (0·1 to 0·2 grm.) is injected in the hope of provoking a positive reaction if the disease is only latent. Naturally, with individual patients the practice must vary, and the above routine is only described as one which has been found to work well in dealing

with large numbers of patients. On no account should one allow the patient to go away without impressing on him the need for careful subsequent observation.

In cases where the Wassermann reaction is found to be positive at the end of the first combined course the most practicable plan appears to be to eommence the next course after six weeks. More salvarsan could be injected, say up to 0·6 grm. in each two weeks, but if it is decided to treat the patient with courses of mercury in conjunction with salvarsan, due regard must be paid to the amount of mercury already administered and the date of the last injection, just as has been found necessary when treating syphilis with intramuscular injections of mercury only.

Neo-Salvarsan or 914 is a condensation product formed by the action of formaldehyde sulphoxylate of sodium on salvarsan. It was introduced by Ehrlich in the hope of overcoming some of the disadvantages of salvarsan. It is an orange-yellow powder which is sent out in sealed capsules like salvarsan. It is very soluble in water, in which it forms a neutral solution, so that there is no necessity to add alkali in its preparation. It is decomposed by physiological salt solution and for this reason was at first administered dissolved in distilled water. It has since been found that it can be dissolved with safety and administered in 0·4 per cent. sodium ehloride solution. It rapidly oxidizes after exposure to air, in this respect being much less stable than salvarsan, and should be administered at once. It is rapidly decomposed if dissolved in water at a temperature above 80°F.; it should therefore be prepared and administered in solution at room temperature.

On the whole it gives rise to less reaction than salvarsan, and if administered at once is less toxic. With regard to dosage, it was at first administered in enormous amounts, e.g. Schreiber gave to robust men on the first day 0·9 grm., on

the third 1·2 grm., on the fifth 1·35 grm., and on the seventh 1·5 grm. On this principle he treated 230 cases, and other workers were giving similarly large doses when a small series of deaths occurred, and it is not now recommended to inject neo-salvarsan in doses any larger than those which correspond to safe doses of salvarsan. In calculating dosage it has to be remembered that three of neo-salvarsan corresponds to two of salvarsan.

The injection may be given in any of the ways recommended for salvarsan. For intramuscular injection 0·5 grm. may be dissolved in 20 c.c. of distilled water, in which it forms a solution which is nearly isotonic. No induration or necrosis follows the injection. To avoid pain 5 c.c. of a 0·5 per cent. solution of novocaine may first be injected, and after a few minutes the neo-salvarsan through the same needle. For intravenous injection 0·9 gram is dissolved in 150 c.c. of 0·4 per cent. sodium chloride solution. The solution can then be injected with the single infusion apparatus already described for salvarsan. The following procedure probably involves the least delay between opening the ampoule and injection of the remedy.

The patient is prepared and the apparatus arranged with 0·4 per cent. salt solution filling the needle and tubing, its upper level being an inch above the bottom of the funnel. The ampoule of neo-salvarsan is then opened and its contents dissolved in the necessary amount of 0·4 per cent. salt solution without any stirring. The solution is poured down the side of the funnel into the salt solution already there and the clip opened to allow the salt solution to flow away till the orange-yellow neo-salvarsan solution appears at the bottom window but one. The clip is then closed, the vein punctured, and the clip reopened to allow the neo-salvarsan solution to flow into the vein. It is followed up with 0·4 per cent. salt solution in a similar manner to that employed with salvarsan.

The action of neo-salvarsan is very similar to that of salvarsan, and it may be given in all cases where the older preparation is indicated.

The advantages of neo-salvarsan are that it is more easily prepared and intravenous injections are slightly less frequently followed by febrile reaction, vomiting, etc., though erythema is rather more common after its use. Its disadvantage is its instability, and I do not think it would be a suitable preparation to use in tropical climates.

On account of the difficulty of reaching the meninges with antisyphilitic remedies administered in the ordinary way, Wechselmann has suggested that neo-salvarsan might with advantage be injected into the spinal canal, since it forms a neutral solution. In this way he gave first 2 c.c. and, after a week, 7 c.c. of a 0·15 per cent. solution to an adult woman who was suffering from syphilis of the central nervous system. No reaction followed, and the patient improved. To another case, a paralytic, he gave 4 c.c. of a 0·15 per cent. solution, and to two infants of two months, 2 c.c. of the same solution without any immediate reaction.

CHAPTER VIII

TREATMENT BY MERCURY—GENERAL REMARKS

Since the introduction of salvarsan the treatment of syphilis by mercury alone may be said to have practically ceased, hence much of the following chapters may appear to be unnecessary, if not indeed antiquated. It must, however, be remembered that for the present, at least, the administration of salvarsan requires a certain amount of specialized skill, and the drug may not always be available. In any case the surgeon will probably still have to employ mercury at some stage of the treatment, and should therefore be thoroughly familiar with its use.

PRECAUTIONS—MERCURIALISM—HOW LONG TO CONTINUE—GENERAL CLASSIFICATION OF PLANS

General Considerations.—When administering mercury for the treatment of syphilis certain fundamental principles must be borne in mind.

(1) The cure is effected by the metal mercury. It may be convenient or even advisable to administer this in the form of a mercurial salt, but the benefit is obtained solely from the amount of metallic mercury absorbed, no matter how this is introduced into the system.

(2) The curative action of mercury has distinct limits, which must be recognized. When a certain amount has been introduced, it ceases to exert a beneficial effect. An

interval of rest must then be allowed. If this is not done, obstinate lesions of the mucous membranes make their appearance and the man's general condition suffers.

(3) Over-treatment is nearly as harmful as under-treatment.

(4) Each case must be treated on its merits; no hard and fast rule can be drawn up which will meet every case. At the same time it is well to have a definite idea of what may be considered a minimum treatment for the average case.

Specific Action of Mercury.—Mercury when absorbed brings about the disappearance of the spirochaetes, it also gains entrance to the special cells of syphilitic lesions and causes the nuclei to separate out, the cell then undergoes fatty degeneration and is absorbed.

Syphilis produces certain changes in the blood, viz., the haemoglobin, number of red blood corpuscles, and the density of the blood are all diminished, while the lymphocytes are increased. Up to a certain point the administration of mercury causes a return to the normal, after which, if the administration is continued, a decrease in the number of red blood corpuscles and of the percentage of haemoglobin sets in.

Rate of Absorption of Mercury.—Mercury can be detected in the urine at the following periods after the administration is begun:—Injections two to three hours; inunctions twenty-four hours; by the mouth on the third day.

Mercury tends to accumulate in the body, especially in the liver and kidneys. It is mainly eliminated by the kidneys, and to a less extent by the intestinal secretions, saliva, bile, milk and sweat. Metallic mercury injected intramuscularly can be recovered from the urine for two to six months after the last injection.

Precautions before and during Treatment by Mercury.—Mercury is a powerful drug and when used in full doses, as in the treatment of syphilis, unpleasant and even fatal consequences may ensue if certain precautions are

neglected. The following are the result of practical experience and must be observed.

(1) *The urine.*—Mercury is mainly excreted by the kidneys, but, if chronic nephritis is present, the excretion is much diminished or indeed ceases altogether. Before beginning treatment, therefore, the first and most important precaution is to examine for albuminuria; if this is found, its cause should be sought for. If due to nephritis, NO MERCURY is to be given till the nephritis has cleared up. If nephritis can be excluded, the albumen may be due to syphilis; in any case, it is well to begin with a very small dose and to examine the urine daily. If the albumen disappears, it may be concluded to be due to syphilis, and full doses can be given. When albuminuria appears for the first time during treatment, it denotes that the maximum safe quantity of mercury has been introduced and the administration must be interrupted for a time. The urine must be examined at intervals to note when the albuminuria disappears, and at least a full month allowed to elapse after this before any further mercury is given.

(2) *The body weight.*—Syphilis in an active form always causes more or less loss of body weight. Mercury, properly administered, results in a gain in weight up to a certain point. If an excessive quantity of mercury is given, the weight again diminishes. The weight must therefore be recorded before commencing a course of treatment and at regular intervals during treatment, and always before every injection. As long as the weight is increasing or remaining stationary the administration may safely be continued, but as soon as the weight shows a steady fall, which cannot be accounted for by any other circumstance, the course must be interrupted and the urine examined for albuminuria. The body weight is, in fact, the most valuable and easily applied guide in regulating the administration of mercury.

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(3) *Teeth and gums.*—Before commencing the treatment, the teeth and gums should be looked at. If the patient is agreeable, it is certainly wise to have stumps removed and carious teeth filled, but when the cleanliness of the teeth is properly attended to, these measures are unnecessary; it is much more important to have all tartar removed, as in spite of careful cleaning, tartar frequently leads to the formation of ulcers. As regards the tooth powder, any kind will do, provided it is used. Some men complain of the tooth brushes being too stiff and causing pain; this can be remedied by soaking the brush in hot water for a few minutes before using it. In the ordinary case no mouth wash is necessary. When ulcers in the mucous membranes of the mouth and fauces are troublesome, a simple and effective plan is to supply the man with tabloids of chlorate of potassium, and tell him to suck one, two or three times a day; this he will usually do, as the painful ulcer does not permit him to forget its existence. If an astringent mouth wash is thought advisable, ordinary alum, 10 grains to the ounce of water, or infusion of quassia, is all that is required. The acetate of alum used at Aachen is very good but rarely necessary. This is prepared by dissolving 1 ounce of alum in 5 of water and 1 ounce of lead acetate in a similar quantity of water, the solutions are then mixed and filtered. The filtrate contains acetate of alum. This is diluted with 10 parts of water, and a few drops of an aromatic essence added to flavour it.

(4) *Recent diseases.*—Men who have recently suffered from dysentery, severe diarrhœa, congestion of the liver, malarial fever or any debilitating disease, are not good subjects for mercurial treatment, and the administration should therefore be commenced with greatly reduced doses and the effect on the body weight noted. Cases of malignant syphilis, i.e. those in which what are usually described as tertiary symptoms appear very early in the course of the disease, do

not tolerate mercury well, and it must be given sparingly at first. Lang of Vienna treated these cases with sarsaparilla alone, till the general health has improved and the symptoms of syphilis have become less marked.

One or two other cautions are usually given, such as avoiding smoking. When dealing with the soldier it is difficult to make him give up smoking, and in most cases, unless the mouth and throat are affected, it is hardly necessary to insist on this. As regards diet, syphilis leads to considerable tissue waste and a liberal diet should therefore be given. Alcohol is rarely necessary, indeed most syphilitics are better without it. Over-indulgence in any alcoholic beverages has a most harmful effect on the course of the disease, in fact, as one authority used to express it, " You can preserve your syphilis in alcohol." When mercury is given by the mouth indigestible articles of diet, or any which are likely to cause gastro-intestinal irritation, must be avoided; when inunctions or injections are being used diarrhœa is much less likely to occur, and dietary precautions are not so important. The general health should be as well maintained as possible. Outdoor exercise and the playing of games are to be encouraged, but at the same time over-fatigue is harmful.

Mercurialism.—This may occur when any form of mercurial treatment is employed, and the longer the periods for which the drug is administered without intervals of non-treatment, the more likely is mercurial poisoning to occur; similarly the more energetic the form of treatment, the more probable is it that the system may become overcharged. Weekly injections of cream continued for months are almost certain to produce a condition of mercurial poisoning, varying in severity with the amount of mercury introduced and the man's resisting powers. The earliest sign is loss of body weight, followed sooner or later by albuminuria; another quoted by Feibes of Aachen is cardiac palpitation; anaemia

is usually noticeable. Stomatitis is however the symptom which usually draws the medical officer's attention to the fact that something is wrong and necessitates the man's admission to hospital for treatment.

As regards treatment, the first thing to do is to stop the further administration of mercury ; if the kidneys are excreting the drug the man will soon recover. The most effective plan of getting rid of the mercury and improving the man's condition is by the use of hot-air baths. Very few military hospitals are supplied with these, but they can be improvised by raising the bedclothes on a cradle and inserting the nozzle of a bronchitis kettle. A temperature of 180°F. for 20 minutes should be employed at least three times a week, each sitting to be followed by a brisk rub with a hot bath towel and change of clothing as soon as perspiration has ceased.

Gaucher recommends natural sulphur waters twice a day for this condition ; small doses of the alkaline sulphates are also well spoken of.

Mercurial Stasis.—In this condition any mercury which has been introduced into the body is not absorbed, while at the same time the manifestations of syphilis are unaffected. Various explanations have been given. Gaucher thinks that the condition is due to the mercury forming an irritating compound which therefore does not circulate freely. He prescribes natural sulphurous waters, with the idea that the mercury is converted into a non-irritating sulphate and so allowed to circulate and exert its influence. A more probable explanation is that the excretory glands, especially the kidneys, are at fault. If undetected and the injection of mercury is proceeded with, after a time absorption recommences with alarming or fatal results, owing to the large quantity which has accumulated in the tissues. The only absolutely reliable way of checking the elimination of mercury, and ensuring that no accumulation is taking place, is by estimating the

quantity of mercury excreted in the urine. Unfortunately, the test for mercury in the urine is, owing to the minute quantity in any specimen, a somewhat troublesome and delicate operation.

The following test may be attempted :—

Take about 10 ounces of the morning urine, acidulate strongly with nitric acid and boil for a quarter of an hour. Then place a very small piece of clean copper foil in the neck of a small-sized funnel so as to nearly plug the opening. Pour the urine into this funnel ; and allow it to escape drop by drop over the copper. Mercury if present is deposited on the copper ; it can then be volatilized by heating the copper in a glass tube. Or a minute piece of copper may be placed in the urine and left for twenty-four hours, the urine being kept warm during this time ; any mercury in the urine is deposited on the copper, which if polished shows a metallic mirror. If volatilized in the presence of iodine, crystals of the red iodide are formed.

Practical Rules.—We must now consider some very important practical points. These are :—

(1) When should the administration of mercury be commenced.

(2) How long should the administration be continued ?

(3) The general scheme of treatment.

(1) **Commencement of Treatment.**—Treatment should commence as soon as a diagnosis of syphilis is made, but not before, as the administration of mercury will either very much modify or altogether prevent the appearance of further symptoms. Hence if the surgeon commences treatment while still uncertain of his diagnosis, he must as soon as possible have the patient's serum reaction tested. For the patient's future welfare it is absolutely essential to settle definitely whether he is suffering from syphilis or not, and with modern facilities there should be no difficulty in

doing so, although it may not be feasible at the time when treatment is begun. To give a short course of mercury, just sufficient to postpone the appearance of definite manifestations of the disease, and then to leave the patient without further treatment or the knowledge that this is necessary, is to expose him to the risk of some grave relapse in the future when it is too late to repair the damage by any form of treatment.

(2) **When Syphilis is treated by Mercury alone, for what Period should the Administration of Mercury be continued ?**—Expert opinions on this question differ widely ; in France, Fournier's views, viz., that treatment should be continued (with intervals) for a period of six years, are generally accepted. In Germany, on the other hand, four years is usually considered sufficient, while in England most authorities are satisfied with two years' treatment. In the army, owing to frequent changes of station, which affect medical officers as well as men, it is difficult to follow up a man's movements and maintain treatment for more than two years. Now if two years be accepted as a sufficient period of treatment, what is its value in curing syphilis ?

Clinically we may take as a test the relative frequency with which tertiary symptoms occur among the cases which have been treated for varying periods and by different methods. Marschalko collected some valuable statistics on this question. His figures were taken from the larger dermatological cliniques of Germany, hence the incidence of tertiary syphilis is somewhat under-estimated, as many cases of visceral syphilis would not be included. The returns of Professor Neisser's clinique showed that of all cases which were treated on the "chronic intermittent" system for two or more years only 1·96 per cent. developed tertiary syphilis. Fournier's figures gave 3·45 per cent. of tertiary syphilis after two years' treatment. From a statistical point

of view Neisser's cases were somewhat few in number, as only carefully recorded ones were included; most of these were treated by inunction. Fournier's figures included a much larger number of cases, mainly treated by pills.

Taking the above figures as our basis and allowing for the occurrence of visceral syphilis, it may fairly be assumed that if we adopt a two years' treatment as our working rule, the proportion of tertiary syphilis, i.e. failures, should not exceed 5 per cent. of the number who contract syphilis, and at least one-third of those failures will not be manifested till after the expiry of the soldiers' contract with the state. From a service point of view, therefore, we may hope to cure at least 95 per cent. of those who contract the disease, i.e. while in the army and reserve they will not show any further signs of the disease, and of the remaining 5 per cent. who may be expected to show some further signs of late syphilis, at least one-half will yield to treatment and be able to continue in the army and do their duty.

The two years' scheme of treatment was introduced in the army in 1905, and may be considered to have been more or less thoroughly carried out from 1906. The statistics for syphilis in the army certainly show a great improvement during this period, but there are so many factors which may have contributed to this lessened incidence of syphilis that it is impossible to estimate the proper share due to the introduction of the two years' course of treatment.

With the object of testing the value of the two years' treatment by mercury, Major L. W. Harrison obtained specimens of blood from 283 patients who had completed the full course of treatment by injections of mercurial cream, receiving in that time 27 grains of metallic mercury. Of these bloods 42 per cent. gave a positive reaction to the original Wassermann test and 75 per cent. were positive by Stern's modification. We are thus forced to conclude that under the

two years' system adopted in 1905 about half of the cases are not really cured of syphilis, although clinically they were well and doing full military duty.

(3) **General Scheme of Treatment.**—With regard to methods of administration, duration of treatment, and the amount of mercury necessary, opinions vary widely. Speaking generally, two schools of treatment exist at the present time—

(*a*) The continuous school, who prefer to give a course of mercury for a definite period continuously, or with short interruptions only.

(*b*) The intermittent school, who give mercury for certain periods separated by intervals which are, taken as a whole, of longer duration than the periods of treatment.

The continuous school may be further subdivided into—

(1) Those who give as much mercury as the patient can tolerate during the whole period of treatment.

(2) Those who diminish the dose of mercury as the manifestations of the disease disappear.

Broadly speaking, the continuous school embraces English and American physicians.

The intermittent school may also be subdivided into—

(1) The periodic intermittent school: those who give definite courses of mercury at regular intervals, irrespective of the manifestations of the discase. (Most of the French, many of the German and other continental experts are embraced in this group.)

(2) The symptomatic school: those who prescribe courses of mercury only when the symptoms of the disease are manifested. (Professor Lang of Vienna, his pupils, Professor Havas, and other Austrians and Germans prescribe treatment in this way.)

The continuous school prescribe mercury in some "mild"

form, such as pills, and aim at keeping the patient continuously under the influence of mercury for a considerable period, with the idea that each recrudescence of the disease is at once nipped in the bud, till the virus becomes completely exhausted and a cure is obtained.

The periodic intermittent school, on the contrary, begin treatment by making a vigorous attack (called "traitement d'assaut" by the French) on the disease, with the idea of crippling it at the start. A period of rest is then allowed, to permit the system to recover from the poison of the disease and the effects of the mercury. Subsequent courses are ordered to forestall the phases of recrudescence which experience has shown may be expected to occur at certain times after the administration has ceased.

Good clinical results may be obtained by following either plan, but if the continuous one is adopted the patient must be trusted to take his medicine himself, a condition which is rarely fulfilled in army practice. The periodic intermittent plan presents the great advantage that the treatment is entirely under the control of the surgeon, and that very many fewer attendances are necessary, thus making much less demand on the surgeon's time as well as the soldier's, and consequently not interfering with his military duties to the same extent as when the continuous plan is employed.

CHAPTER IX

SYPHILIS: METHODS OF ADMINISTERING MERCURY—MOUTH—INUNCTION—INJECTION OF SOLUBLE SALTS

THE various methods of prescribing mercury may be divided into two main classes, the "MILD" and the "ENERGETIC." The former are indicated when for any reason it is desired to exercise only a moderate mercurial influence, possibly for a considerable period, but when the choice is in no way restricted the energetic methods can be used on the periodic intermittent scheme and yield very satisfactory results, without necessitating so many attendances on the part of the sufferer or such constant supervision by the medical officer. The superiority of the energetic plans, from an army point of view, if not indeed in a civilian practice too, is at once evident. The various methods may be grouped in tabular form as follows:—

	MILD.	ENERGETIC.
1. By the mouth.	Pills,* powders,* mixtures.*	None.
2. By the skin	(1) Welander's bag. (2) Calomel plasters. (3) Mercurial ointment on lint, binders or socks. (4) Perchloride baths, with or without galvanism.	(1)* Inunction with mercurial ointment. (2) Calomel vapour baths.

	Mild.	Energetic.
3. By the rectum.	Mercurial suppositories.	—
4. By injection.	(1) Soluble salts in reduced doses.	(1) Intravenous. (2) * Intramuscular of soluble salts in full doses. (3) * Intramuscular of mercurial cream. (4) * Intramuscular of the insoluble salts.

The methods which are marked with a * are suitable for the treatment of syphilis throughout the whole course of the disease, the others could no doubt be so used, but are of special advantage when some particular lesion has to be treated.

1. **By the Mouth.**—The administration of mercury by the mouth commends itself to many surgeons and it undoubtedly possesses several advantages; thus it is clean and does not lead to soiling of the surgeon's hands or the patient's clothing. It is painless and therefore not objected to by patients, and as the patient is entrusted with the taking of the remedy himself, it entails the minimum of trouble for the surgeon. Against these advantages, however, must be set certain disadvantages. Absorption is slow, as shown by the time taken before mercury appears in the urine. It is a mild form of treatment and in the severe cases contracted in the tropics it rarely exerts a beneficial effect. In order to obtain a cure the administration must be continued for much longer periods without any intermission, as the effect of the drug is soon exhausted. There is considerable risk of setting up gastro-intestinal irritation, especially if large doses are employed; if this happens, treatment must either

be stopped for a time or some other drug, such as opium, which is not necessary for the cure of the disease, must be added to the prescription. Again, in army practice it is most difficult to ensure that the medicine is regularly taken ; this is, indeed, the greatest objection to this plan. (For Formulae and Scheme see Appendix III.)

Inunction.—When properly carried out treatment by inunction is one of the best ways of curing syphilis, but if patients are allowed to use their own discretion as to dosage, duration of rubbing, etc., the results, as might be expected, are very unsatisfactory. An important point is to have a clean, soft skin. At Aachen, the great centre for inunction, natural sulphur water baths are used. Where natural waters are not obtainable, an ordinary hot bath is quite sufficient for the purpose. A very fair sulphur bath may be prepared by adding 1 to 2 ounces of the liquor calcis sulphurata to the ordinary full bath. When facilities for hot baths are wanting the directions given below as to washing must be carried out, if not, a sharp attack of dermatitis is almost sure to follow.

When out-patients are treated by this method, each man must set apart two sets of woollen underclothing. During the course one of these is to be worn night and day for a week, then changed, and the soiled one sent to the wash ; the clothing will probably be badly stained by the ointment. The general directions must be carefully adhered to in the case of out-patients.

The following plan of treatment for use in hospitals has been carried out and can be recommended :—

(1) Before the inunction is performed a hot bath is given for 20 minutes. When baths are not obtainable the patients must be directed to wash their hands, the part of the body to be rubbed, and the part rubbed on the previous day, before carrying out the inunction.

(2) The following is a useful and easily prepared formula for the ointment :—

R Ung. hydrarg.	gr. 40
Adipis lanae (B.P.)	gr. 20

Mix thoroughly and wrap in wax paper. One packet to be used for each rubbing.

These packets should be handed out by the medical officer to each patient, the time noted, and directions given as to how long the inunction is to be continued ; each patient rubs himself ; when the back is to be done the men sit in a circle and each man rubs the back of the man in front of him. The rubbing should be done slowly, exerting considerable pressure so as to force the ointment into the skin, and in cold weather the men should sit in front of a fire. A non-commissioned officer, or trained orderly, should be told off to watch the men.

When the prescribed time has passed, the medical officer must himself inspect the men before dismissing them to wash their hands. When properly done the skin should look as if it had been rubbed over with blacklead, not shiny and greasy. If there is any doubt as to whether the man has properly rubbed himself or not, the medical officer should order a further period of say 10 minutes' rubbing, and watch the patient do this.

(3) The inunction is to be performed daily for 20 or 30 minutes. The course of inunctions is usually 42, but the number may be increased or diminished to suit individual cases.

(4) The parts are to be rubbed in the following order :— First day, both calves ; second day, both thighs, avoiding the hairy parts ; third day, the abdomen ; fourth day, both forearms. If the inunction is used on the back, the application must be made by another patient, or by a trained orderly.

(5) Special flannel underclothing (condemned sets do well

for this purpose) should be worn night and day for a week at a time during treatment. (For plan of treatment see Appendix IV.)

Intramuscular Injection.—This method presents many advantages, and from an army point of view is undoubtedly the best. The treatment is entirely under the surgeon's control, the quantity of mercury introduced can be accurately measured, and provided ordinary precautions are observed there is no danger.

Many preparations have been advocated at different times, but all of these fall into two main classes, the soluble and the insoluble.

At first sight the soluble salts present many attractions. Thus the solution can be prepared anywhere without special apparatus and at a moment's notice, so that if desired mercurial treatment can be begun at once, as no special syringe or needle is necessary. The solution can be injected into any region, and there is no danger of embolism occurring.

When, however, it is a question of treating a case of syphilis by the injection of soluble salts, disadvantages are at once apparent. The most important of these is the fact that the quantity of mercury which can safely be introduced at one injection is very small. Take the perchloride of mercury, one-third of a grain is about as much as it is wise to use in one injection—this only contains one quarter of a grain of metallic mercury as against the 1 or 1½ grains in each injection of mercurial cream. Hence if energetic treatment of syphilis is desired, the injection must be frequently repeated. The second objection to the soluble salts for the routine treatment of syphilis is that all of them cause more or less pain, in fact the amount of pain is excessive having regard to the small quantity of mercury introduced. The pain and frequent repetition of injection reduces the soluble salts to a much lower level of efficiency than the insoluble salts or cream.

If it is determined to use soluble salts, one of the most efficient and readily obtained is the perchloride of mercury. The following is a useful formula :—

R Hydrarg. Perchlor	. . . .	8 grains.
Sodii Chloridi	. . . . .	4 grains.
Aq. Destill	. . . . .	400 minims.

Dissolve the chloride of sodium in the water and filter, to remove particles of dust, then add the perchloride of mercury.

Minims 10 for each injection ; this contains one-fifth of a grain of perchloride = a little more than one-seventh of a grain of metallic mercury. Using the above dose, a scheme of treatment as follows is suggested ; it must, however, be borne in mind that this scheme can in no way be regarded as being equally efficient with the scheme of treatment by injections of mercurial cream.

First Course—

Three injections a week for two weeks

= 6 injects. = 6/5 gr. $HgCl_2$ = ·87 gr. Hydrarg.

Two injections a week for six weeks

= 12 injects. = 12/5 gr. $HgCl_2$ = 1·75 gr. Hydrarg.

Interval of one month.

Second Course—

Two injections a week for eight weeks

= 16 injects. = 16/5 gr. $HgCl_2$ = 2·36 gr. Hydrarg.

During the remainder of the first year, the same plan to be continued, i.e. treatment to be administered for two consecutive months followed by an interval of non-treatment of one month. During the second year the treatment to be given for one month in each quarter of the year. This plan, if adopted, works out to the following results :—

In the first year treatment would occupy 32 weeks, and during the second year 16 weeks. The total number of injections would be 98, or if two additional ones were given, 100. The total quantity of perchloride injected would be 20 grains

containing very nearly 15 grains of metallic mercury. The above plan is probably as much as is given on any scheme for injecting soluble salts, yet when the number of injections required to introduce 15 grains of metallic mercury is contrasted with the 27 grains of metallic mercury injected in 27 injections when the cream is used, the superiority of the latter is at once evident.

The biniodide of mercury is strongly recommended by Lévy-Bing, who gives the following formula :—

℞ Biniodide of mercury . . .	2 grains.
Pure iodide of sodium . . .	2 grains.
Sodium chloride	$\frac{3}{4}$ grain.
Distilled water	100 minims.

Ten minims for each injection ; this quantity of the solution contains one-fifth of a grain of the biniodide. The percentage of mercury in this salt is 44·05, so that 10 minims of the above solution contain approximately ·08 grains of metallic mercury, a somewhat low dose. Lévy-Bing recommends 1 c.c. (= 17 minims) for each injection, and states that the dose may be increased to twice or even two and a half times this amount without any danger ; he believes this preparation to be a very useful one in secondary or tertiary syphilis, and nearly equal to calomel injections in efficiency.

Many other soluble salts have been tried, but almost all of them possess some serious objection, and it is hardly worth while to enumerate them here.

CHAPTER X

SYPHILIS: INJECTION OF CREAM—INSOLUBLE SALTS—INTRAVENOUS AND OTHER METHODS

Intramuscular Injection of Mercurial Cream.—For army purposes this is the most suitable method of treating syphilis, and it is undoubtedly one of the most efficient. The several points will now be considered in detail.

(*a*) *The cream.*—In the *R.A.M.C. Journal* for July, 1906, there is an excellent article describing the difficulties in making an ideal cream. From the surgeon's point of view the essentials of a good cream are:—

(1) That the mercury be finely subdivided and evenly distributed through the mixture.

(2) That the cream be stable, that is, that in the intervals between use no special precautions, such as standing on ice, should be necessary to prevent the mercury from separating out.

(3) That the cream be sufficiently fluid for injecting, without having to warm it before use.

(4) That the cream be of moderate concentration, 1 grain of mercury in 5 minims of cream is a good working strength. This permits of the dose being regulated to whatever the surgeon may desire, does not introduce unnecessarily large quantities of inert foreign matter, does not make a bulky injection, thus avoiding mechanical pressure at the site of injection, and most important does not necessitate constant refill-

ing of the syringe when a large number of injections have to be given.

No antiseptic substance need be added, as the cream is sterile and remains so. By having two creams (a hot and a cold weather one), of different composition but the same strength, and using the special paraffin instead of the liquid paraffin, the above desiderata can for practical purposes be obtained.

For formulae see Appendix V.

Dosage.—In order to determine the most advantageous dose of mercury when treating syphilis by injections of grey oil, Barthélemy and other authorities in Paris made a series of scientific observations. The therapeutic value of the dose was gauged by estimating its effect on the condition of the blood, urinary excretion and the patient's weight. Their conclusions may be summed up as follows :—

The quantity of mercury injected should bear a definite relation to the patient's weight ; thus for an ordinary (French) man weighing 8 to 9 stone, they found that 8 to 9 centigrammes of metallic mercury (7 cgm. = 1 grain nearly) injected once a week, for six weeks, gave the best results ; after the fifth injection there was a tendency for the red blood corpuscles to diminish and if more than six injections were given the haemoglobin decreased also. Following this course of six injections an interval of non-treatment for two months was necessary. In the case of a big man weighing 13 stone the dose may with advantage be increased to 14 or even 16 cgm. a week (2 to 2¼ grains). As much as 25 cgm. (3½ grains) have been given as a single injection without any unpleasant symptoms ensuing ; as a general rule, however, it is not advisable to exceed the doses they recommend, which are well within the limits of safety, and quite sufficient to meet all therapeutic requirements. Applying Barthélemy's rules to the British soldier, who usually weighs at least 10 stone, we

may with safety give an injection of 10 cgm. (= $1\frac{1}{2}$ grains of metallic mercury) once a week for six weeks. A weekly dose of 1 grain is sufficient if continued for nine weeks instead of six, but a dose of $1\frac{1}{2}$ grains is certainly not a dangerous one, and in the later courses it has the great advantage of allowing longer intervals between the courses with fewer injections in each, thus not making so great a demand on the soldier's or the surgeon's time.

Syringe and Needle.—The most suitable syringe for injecting cream is an all-glass one with a platino-iridium needle of rather large bore.

For sterilizing the needle, heated olive oil is the safest and most convenient agent. It is not necessary to drop in bread crumbs to show when the oil has attained the proper temperature, for soon after the lamp is in position quickly-moving currents appear in the oil, and a hot pungent smell is given off. The temperature of the oil is then between 120° and 140°C. Chemical solutions are not satisfactory when an oily mixture is to be injected. The needles must not be heated in the naked flame, as this melts the soldering and ruins the needle.

Before filling the syringe the cream must be well stirred with a glass rod, which has been passed slowly through the flame to burn off the adherent cotton filaments, and prevent these from being introduced into the cream. The cream must not be left uncovered for a longer period than is absolutely necessary, as this allows particles of dust to enter.

Preparation of the Skin.—Careful measures must be taken to render the skin aseptic or as nearly so as possible; neglect of this precaution will almost certainly lead to severe septic inflammation, owing to particles of infected epithelium being pushed into the subcutaneous tissue by the point of the needle.

A simple and effective method of preparing the skin is to take a piece of sal alembroth wool well moistened with

methylated spirits, and rub the selected part till a red blush appears, showing that all the dead epithelium has been removed.

Site of Injection.—The best place in which to make the injection is undoubtedly the upper part of the buttock, for here the subcutaneous tissue is thick, with a deep layer of muscle underneath. The only risk lies in penetrating one of the vessels, which are however less numerous above the level of the great trochanter. A good working rule is to keep to the level of the junction of the gluteal folds, making the first injection one inch to the left of this, the second one inch to the right, the third two inches to the left, the fourth two inches to the right, and so on. In this way no two injections are made at the same spot and each buttock is taken alternately.

If for any reason the buttock is not available, a spot one inch from the middle line on either side of the vertebral column may be selected ; the suprascapular fossae, or even the deltoids, may be made use of in the case of a patient confined to bed. When choosing any site, the points to be observed are that the subcutaneous tissue be thick and the parts not subject to free movements, thus the thighs are not to be recommended.

Technique of Injection.—The skin having been prepared and the syringe and needle sterilized, fill the syringe, attach the needle and push the piston lightly, in order to fill the needle, then dip the point of the needle into the heated oil to remove the drop of cream which always exudes and which if deposited in the skin at the point of entry gives rise to a painful spot. Next thrust the needle into the selected spot to its full extent and detach the syringe or pull on the piston. If a vein has been penetrated blood will flow from the needle within a second or two, in which case a fresh site must be selected ; if no blood flows the syringe may be re-

attached and the injection completed. If the injection is made into a vein a fat embolism is produced with somewhat alarming symptoms such as fainting, intense dyspnoea, etc. These usually clear up with rest, and no fatal results follow. When choosing the actual site of puncture avoid pimples, as these if injured always bleed rather freely and soil the soldier's clothing; and it is also well to avoid hairs, as these may be forced into the skin. A carbolized "glass" cloth should be spread out on the table for the surgeon to wipe his fingers on, if necessary, or on which the syringe may be laid for a moment if desired. "Glass" cloth is of firmer texture than lint, so that if accidentally touched by an oily finger few if any filaments stick to the operator's hand.

After Effects of Injection.—An injection of mercurial cream is always followed by more or less inflammation; this may be of mild degree and merely be the result of chemical or mechanical irritation; on the other hand, when due to the introduction of septic infection the inflammation may be of an extremely severe type and lead to most unpleasant consequences.

The non-septic sequelae are:—

(1) When cream is deposited in the true skin at the point of entrance of the needle a superficial painful swelling, lasting a few days, may result.

(2) About the fourth day after the injection a small deep-seated nodule can generally be felt at the spot where the cream was deposited; this is not painful unless subjected to great pressure. It usually becomes absorbed about the tenth day following the injection.

(3) Sometimes a considerable amount of very painful induration is formed at the site of the injection; this is probably due to the introduction of foreign matter, such as particles of dust, cotton filaments, etc.

(4) Occasionally neuralgic pain along the great sciatic

nerve is complained of ; this varies in intensity but is rarely severe and disappears in the course of a few days. The pain is probably due to the cream being deposited on one of the lesser nerve filaments.

Mercurial cream is sterile, hence when septic troubles follow an injection, either the needle or the skin must be held responsible. When the infection penetrates only as far as the true skin, a superficial swelling, somewhat resembling a boil, ensues ; this may resolve, or break down, leaving an unhealthy ulcer which slowly heals.

If the subcutaneous tissue becomes infected a very extensive abscess may form between the muscles and superficial tissues. This requires the usual surgical treatment.

Scheme of Treatment by Injections of Mercurial Cream.—When treating syphilis by injections of mercurial cream, the danger of over-dosing and its serious consequences must be borne in mind. Surgeons who regularly use this method of treating syphilis will soon evolve a scheme of their own. For the guidance of those who have not had much experience a tabular scheme is given in Appendix V. This is based on the results of the serum reactions obtained in a number of men who had completed a full course of treatment, consisting of 27 injections of mercurial cream (containing a total of 27 grains of mercury) in two years. The serum reactions show that this treatment is insufficient for the average case ; under the scheme now suggested each man will receive 40 grains of mercury in the first two years of treatment. It need not be followed exactly if the surgeon has any reason for altering it, thus he may prefer to give smaller doses with shorter intervals between the courses. In no case, however, should weekly injections be continued for more than two months at a time ; if a dose of 1½ grains be employed, *six weekly* injections is the *maximum* permissible course. When a dose of 1 grain is given the course must not

exceed nine weeks. An interval of at least six weeks must then be allowed to elapse before injections are recommenced. Neglect of this simple precaution has, in many instances, been followed by severe stomatitis or even more unpleasant consequences.

During the first two intervals, the patient is to be inspected at least once a fortnight; during the third, if no fresh manifestations have appeared, he may be inspected only once a month.

If fresh manifestations should appear during the second or third intervals, these may be shortened and an additional course given, provided there is no albuminuria. (For Formulae and Scheme see Appendix V.)

Insoluble Salts.—Many insoluble salts of mercury have been tried in the treatment of syphilis; very few of these, however, present any special advantage, and the only one which is worthy of notice is calomel. Injections of calomel form one of the best methods of treating syphilis; unfortunately it possesses several marked disadvantages. One of these is that the injections may be followed by very severe pain, and if strict asepsis is not maintained an abscess will probably form at the site of injection. Another objection to its use is that on account of its high molecular weight it does not lend itself to the preparation of a satisfactory emulsion. Colonel Lambkin's cream (*see* Appendix V) has to a great extent obviated these objections, as the creo-camph acts as an efficient analgesic while the palmitin basis, if not overheated, is sufficiently dense to suspend the calomel. When using it the needle must be heated before each injection, as otherwise the cream will solidify and block it.

In obstinate cases, or those in which the central nervous system is attacked and it is imperative to bring the disease under control at the earliest possible moment, it may be worth while to try injections of calomel, in spite of its draw-

backs. As a routine method of treatment, however, its disadvantages far outweigh its advantages, and place it much below mercurial cream.

A preparation, largely used in Germany, is the salicylate of mercury. The following is a convenient formula :—

Hydrarg. salicylat.	grs. x.
Paraffinum liquidum	m. 100.

10 to 15 minims to be injected once a week.

This salt must be finely triturated before being mixed with the paraffin, so as not to block the needle. The special advantages of this preparation are (1) it can be prepared by simply mixing with the paraffin, no prolonged stirring being necessary ; (2) it can be sterilized by heat as often as required, without undergoing alteration ; (3) vigorous shaking before use is all that is required to ensure proper consistency of the mixture ; (4) it is not affected by heat or cold, and is therefore suitable for use in any climate without special precautions to ensure its remaining fit for immediate use. It is not so active as the mercurial creams or grey oils, but is sufficiently so for use in the later courses.

The following plans of treatment are what might be called " occasional " methods, by which is meant that these sometimes offer special advantages in particular manifestations of the disease, but are not to be recommended for routine use in all cases.

Intravenous Injection.—This method was first described by Bacelli in 1893, and was extensively tried by Ernest Lane. The following description is taken from his paper in the *British Medical Journal* of 1896.

The skin of the arm having been carefully sterilized, apply a bandage above the vein selected, in order to render this prominent. Twenty minims of a 1 per cent. solution of cyanide of mercury (or a similar solution of perchloride of mercury can be used) are then drawn up into a sterilized

syringe having a fine platino-iridium needle, the needle is then thrust obliquely into the vein and the point is moved about to make sure that it is free within the lumen of the vessel (it is very easy to transfix the entire vessel); the bandage is then removed and the solution slowly injected. Provided the injection is made into the lumen of the vessel and not into the surrounding connective tissue, no inflammation or other disturbance is experienced. If the veins are very small, the injections cannot be carried out.

This method is undoubtedly one of the most rapid for obtaining an antisyphilitic effect, and in urgent cases, such as lesions of the central nervous system, it may be of great service. As a routine method of treatment it does not offer sufficiently great advantages.

Calomel Vapour Baths.—This method was formerly largely used, but has lately been rather neglected in favour of the more accurate and less troublesome plans which we now possess. Sometimes an obstinate syphilide will yield rapidly to calomel fumigation; it is, however, a fairly energetic method of prescribing mercury and hence must not be used concurrently with other plans.

Half a drachm of calomel should be sublimed at each sitting, using Lee's apparatus; two or at most three sittings a week should be prescribed, preferably in the evening, so that the patient can get into bed (in blankets) at once, while the skin is still warm from the hot air.

Welander's Mercurial Bag.—This is a mild method and especially indicated for adults who may happen to contract some severe illness, such as Malta fever, during the early stage of syphilis and while mercurial treatment is still necessary; it is also useful for pregnant women who are near term, or for congenital syphilitic children.

A cotton bag is made large enough to cover the whole front of the chest, leaving the upper seam open. This is turned

inside out each morning, and a drachm of mercurial ointment (B.P.) is spread on the inner surface of one side; the bag is then inverted and worn night and day with the prepared side next to the skin; at the end of a fortnight a new bag is taken into use. The course should last for a month at a time.

Blaschko introduced a special fabric called "mercolint," which is merely cotton impregnated with mercurial ointment, a sheet of this being worn inside a vest: this has the disadvantage that the mercury is not replaced as it becomes vaporized.

Calomel plasters containing roughly 25 per cent. of calomel in diachylon plaster were introduced by Quinquaud; a piece 4 inches square is applied to the skin and worn for a week. These do not seem to possess any special advantage. Lang spreads a drachm of mercurial ointment on the skin at night, applies a bandage over this and washes the skin in the morning.

Similarly mercurial ointment has been placed on binders, and allowed to rub itself into the skin by the body movements during the day. This is an ancient way of treating children; it may be used for adults, too, but it must be borne in mind when employing any of these skin methods that if the person is liable to profuse sweating, as the result of his occupation or playing games, absorption becomes very rapid and mild symptoms of mercurialism will appear; hence in these cases the person must be cautioned only to wear the binder at night. Smearing mercurial ointment on the socks is an effective if crude method of introducing mercury; it might be of use on service.

The Mercurial Bath.—Of other methods which have been made use of for the administration of mercury in the treatment of syphilis, the mercurial bath deserves some attention.

In the case of soldiers returning from tropical service, who

may have become debilitated in health from other causes in addition to syphilitic disease, it is not uncommon to find multiple cutaneous syphilitic lesions, showing a marked tendency to necrosis and ulceration. In such cases the use of the bath containing mercury in solution is frequently found to be of service. The drug appears to exert a local curative effect on the cutaneous lesions, in addition to its recognized influence by absorption.

All the precautions directed to be observed during mercurial treatment must be scrupulously observed in the case of such patients.

The mercurial bath may be prepared according to the following prescription :—

Mercuric chloride	60–180 grs.
Ammonium chloride	1–3 drs.
Water (at 100°F.) to	30 gallons.
or	
Mercuric chloride	60–180 grs.
Diluted hydrochloric acid	1 dr.
Water (at 100°F.) to	30 gallons.

The patient may remain in the bath from ten minutes to half an hour. The water in the bath must not be allowed to become too cold, and the patient must not become chilled after the bath. The baths may be continued till the cutaneous lesions have healed, when mercurial treatment may be carried out by other methods appropriate to the case.

Zittman's Treatment.—This form of treatment is especially indicated for elderly or debilitated people of feeble constitution. Good results have been obtained at Netley in the case of soldiers invalided for syphilis from the tropics, especially in those suffering from cutaneous lesions. A hot room is required, and the formula (*see* Appendix VI), is somewhat complicated.

Administration of Mercury per Rectum.—(C. Audry, *Annal. de Dermat. et Syphilis*, March, 1906).—Attention has

been called to a plan of treating syphilis by the administration of mercury per rectum. Each suppository is made up to contain 3 centigrammes of metallic mercury in cacao butter, and one is inserted each evening for a month, after which a few days' rest is allowed. It is claimed for this plan that it possesses all the advantages of administration by the mouth without giving rise to stomatitis or diarrhoea, and that it is therefore suitable for people who are very susceptible to mercurial pills. It is, however, a mild method of treating syphilis and of no use in severe or obstinate cases.

Comparative Values of different Methods of Treatment.—In the British army both medical officers and their patients are liable to frequent changes of station. Different medical officers may naturally prefer different methods of treatment, at the same time it is essential that the treatment of the disease should be carried out systematically. After considering this question and the evidence at their disposal, the Sub-Committee of the Advisory Board drew up the following scale of equivalents, so that a soldier who has been under one form of treatment may, on change of station, continue his treatment by some other method.

(1) One injection of mercurial cream containing $1\frac{1}{2}$ grains (= 10 c.gm.) of metallic mercury, is equivalent to—

(2) Three injections of a soluble salt (say, perchloride of mercury containing one-fifth grain in each injection); or to—

(3) Seven inunctions of mercurial ointment using 20 grains of mercury daily; or to—

(4) Twenty-one pills each containing 2 grains hydrarg. cum creta, three pills administered daily.

The above scale of equivalents represents energetic treatment for one week.

CHAPTER XI

SYPHILIS: IODIDES—SARSAPARILLA—SOME SPECIAL LESIONS —FITNESS FOR SERVICE

The Iodides.—Next to mercury the iodides are the most useful preparation we possess in the treatment of syphilis, but it must be clearly understood that the iodides are in no sense a substitute for mercury even in the late stages of the disease. They are useful all through the disease; thus Lang prescribed small doses of iodide of potassium alone during the very early secondary stage while awaiting the appearance of the eruption; this was to give relief from the headache which so often precedes the general manifestation of the disease, but was in no way looked on as an attempt to treat the disease.

During the so-called secondary period, if the mucous membranes are affected, the beneficial action of mercury is greatly assisted by the simultaneous administration of iodides, while in the later stages of syphilis the absorption of gummatous masses is largely brought about by iodides, which even then, however, should not be relied on alone but used in conjunction with mercury.

The iodides are most usually prescribed as iodide of potassium, sodium or ammonium, or as a combination of all three. The official dose of iodide of potassium or sodium is given as 5 to 20 grains, and, as a general rule, a 10 grain dose three times a day is sufficient; in many cases, however, this dose has been enormously exceeded without any bad results. Some

people are very susceptible to iodine and develop symptoms of iodism with relatively small doses; when the iodism takes the form of an eruption the addition of small quantities of arsenic may serve to prevent this. Iodides should be taken after meals, even then they may give rise to dyspepsia; in these cases a small tumblerful of warm water taken half an hour before eating, by washing away any remains of the iodide adhering to the stomach wall, will often give relief.

Occasionally it may occur that the iodides for some reason cannot be given by the mouth, if so, iodide of potassium in quantities up to a drachm may be successfully administered in 4 ounces of water as an enema. This does not give rise to any irritation, and the therapeutic effect is satisfactory.

Iodine may also be prescribed as the tincture in doses of 10 to 30 minims three times a day in tea or coffee. Iodoform in pills 5 to 15 grains daily has also been used with success. These last two forms of administering iodine are to be looked on as exceptional methods, and only to be employed when the ordinary plans fail to influence the disease. Iod. albacid is a compound of iodine and albumen, containing 10 per cent. of iodine which can be prescribed in pill or tabloid form, 15 grains twice or thrice daily. It is a mild preparation and easily taken; as it keeps well even in the tropics, it is most suitable for patients who have to travel and wish to take a supply of medicine with them.

Iodipin is a compound of iodine and sesame oil, containing 25 per cent. of iodine. It is especially useful in chronic debilitated cases of syphilis, as it does not exercise any depressing effect. Its action is slower than that of iodide of potassium, but its effect is very much more lasting, as after a course of iodipin, iodine can be recovered from the urine up to a year. Feibes of Aachen injects 23 c.c. daily for a month or more. Lambkin injected 10 to 15 c.c. daily for ten days, and reported that this was absolutely painless. The solution requires warm-

ing before use to let it run freely through the needle. Feibes specially recommended it for tertiary syphilis affecting the central nervous system. Iodipin is also made up to contain 10 per cent. of iodine, and can be given in capsules by the mouth.

Plan of Administration.—The iodides of potassium and sodium should not as a general rule be ordered for more than fourteen consecutive days, after which an interval of one week should be allowed. If given continuously for long periods they cease to act beneficially, and, on the contrary, produce marked depression.

Quinine.—Lenzmann and Knapp reported good results from the daily injection of 0·5 grm. of quinine hydrochloride. This might be tried in refractory cases in the tropics.

Tartar Emetic, injected intravenously in 10 cgm. doses daily for 10 days, has also been well reported on; intramuscular injections are excessively painful.

Sarsaparilla.—This drug at one time enjoyed a great reputation as a cure for syphilis, it then fell into disfavour, but has recently been recommended again. It is one of the ingredients of Zittmann's decoction.

Lang used sarsaparilla very largely in the treatment of malignant or cachectic syphilitics, in fact he relied on sarsaparilla to remove the most urgent manifestations of the disease before proceeding to administer any mercury. His formula is as follows:—

Take 30 ounces of sarsaparilla root and macerate for two hours in 200 ounces of water; the solution is then evaporated down to 15 ounces. The dose is 2 to 3 ounces of this concentrated solution daily.

A freshly made infusion is recommended by all writers on this drug in preference to any alcoholic tincture or extract.

On the Treatment of certain Manifestations of

Syphilis.—*The chancre.*—As this is the focus from which the rest of the body becomes infected an attempt should be made to remove it as early as possible. When feasible it should be excised; if this cannot be done without damaging important parts ionization with mercury should be employed. A pad moistened with 1 in 1,000 solution of perchloride of mercury should be applied to the sore and the positive pole of a battery connected with it. A current of 2 to 5 milliampères, the stronger the better, provided it is not too painful for the patient, is then employed for 10 minutes daily. Under this treatment an indurated sore will rapidly diminish in size and hardness.

Lesions of the Mucous Membranes.—The usual lesions met with on the mucous membranes within the cavity of the mouth are, (1) a superficial ulcer on the tonsil; (2) the early mucous patch with a glistening surface, on the lips or tongue—these two are generally early symptoms occurring in untreated cases; (3) the deep painful ulcer on the gums between the teeth, commonly the result of tartar on dirty teeth and a prolonged administration of mercurial pills; (4) the late mucous patch on the tongue, occurring at the site of some chronic irritation such as a sharp tooth after a number of injections have been given continuously without sufficient intervals of rest; (5) bald patches with or without fissures—these appear late in the disease, in cases which have been imperfectly treated and have indulged in excessive smoking or drinking strong spirits; (6) the sloughing gumma of the palate or fauces, seen in debilitated men invalided from the tropics with syphilis. There are certain points common to all of these which require attention. They are, (1) to insist on cleanliness of the mouth and teeth; (2) to remove all sources of irritation and forbid smoking; (3) to give short courses of iodides, which seem to have a specially beneficial action on lesions of the mucous membranes.

As regards mercury in these affections, if none or very little has been given, a full course should be commenced at once, preferably by injections, as pills rarely do much good; when, however, a considerable quantity of mercury has already been introduced, the administration should be at once suspended and an injection of salvarsan given, followed by a short course of iodides.

Local Treatment.—This is by no means always necessary, and if daily applications of strong irritating solutions are employed indiscriminately for every form of lesion of the mucous membranes, more harm than good is sure to result. It may be remarked in passing, that many German authorities do not employ any local treatment for mucous patches, as they regard these as merely an ordinary manifestation of the disease which will yield to constitutional treatment.

(1) The most suitable application for the early superficial ulcer of the tonsil is a solution of about 20 grains of nitrate of silver to the ounce of water, on alternate mornings for a week or so.

(2) The early mucous patch will yield most readily to the following plan: First dry the surface with absorbent cotton wool, then apply a 10 per cent. solution of chromic acid and immediately afterwards either the stick of nitrate of silver or a 25 per cent. solution, on alternate mornings for a week to ten days. The chromic acid sinks into the tissues, where the silver nitrate comes in contact with it and chemical action takes place with an excellent effect on the lesion; if the solutions are allowed to mix outside the tissues they are quite inert. Other remedies which have been recommended are, a 1 per cent. solution of perchloride of mercury in equal parts of rectified spirit and water; tincture of iodine; forty per cent. solution of zinc chloride; acid nitrate of mercury: the last two seem to be unnecessarily severe for the purpose.

(3) The deep painful ulcer of the gums is to be thoroughly

cleansed by spraying with peroxide of hydrogen, after the tartar has been removed ; next the surface is to be anaesthetized with a 10 per cent. solution of cocaine, and then well swabbed with acid nitrate of mercury B.P., or a 40 per cent. solution of zinc chloride. In all these three conditions the most important local treatment consists in frequently washing the mouth with water as hot as can be borne by the man ; in fact this, together with constitutional treatment, will often get rid of the trouble in a few days.

(4) The late mucous patch of dirty white epithelium rarely requires any special treatment beyond the removal of the source of irritation, and the same may be said of

(5) The bald patches, provided the general treatment has been properly carried out.

(6) The sloughing gumma of the palate or fauces must be thoroughly sprayed with peroxide of hydrogen ; this converts the sloughy membrane into a creamy froth, which can be washed away with a gargle, leaving a fresh surface to which any mild antiseptic may be applied ; as long as the membrane is left, no drug can reach the diseased surface underneath. Calomel volatilized by heat and blown on to the clean surface is an excellent application ; a special apparatus is required.

Obstinate Cutaneous Syphilides.—Some syphilides, such as the small follicular and squamous palmar syphilides, are most refractory to treatment ; in these cases a mercurial ointment rubbed in locally will often hasten absorption. The white precipitate ointment of the B.P., diluted with an equal part of lanoline, the mercurial ointment similarly reduced to half its strength, or the oleate ointment, are suitable for this purpose.

Gummata.—Sometimes indolent gummatous ulcers are met with on the surface of the body, which do not respond to local treatment, such as scraping and the application of ointments. These will frequently take on a healthy action

after one application of blistering fluid, when ionization with perchloride of mercury or the application of calomel vapour should be tried. If this fails surgical treatment, i.e. the excision of the whole ulcer with suturing of the edges, may be tried, or, if too extensive for this, the surface should be refreshed with a sharp scalpel, and the cavity packed with some stimulating preparation, such as oil of turpentine.

Fitness for Service while under Treatment.—*At Home.*—As long as the primary sore remains unhealed the man should be kept in hospital, to avoid the risk of infecting his comrades in the barrack room. With this exception it may be taken that, as a general rule, men undergoing treatment are fit for all duty at home, and indeed do much better if employed in the open air than if shut up in hospital. A few will require readmission, either on account of some infective lesion, such as mucous patches appearing early in the course of treatment, or on account of some lesion like iritis, which demands indoor treatment; the percentage of readmissions is, however, small, and likely to become less with our increasing experience in the continuous treatment of syphilis.

Service Abroad.—With few exceptions syphilis will yield to careful treatment in any climate; if therefore energetic treatment has been carried out for at least three months, and the serum reaction has become negative or weakly positive, there is no reason why a man should not be considered fit for service in most stations abroad; the main exception is West Africa, to which, because of its very debilitating climate, no man should be sent till he is looked on as cured. If, on the other hand, the disease does not respond to treatment, and the man has several readmissions for manifestations while undergoing treatment, and his serum reaction remains positive, it would not be wise to send him out of the United Kingdom.

Active Service.—To be passed fit for active service, a man

should have completed one year under treatment and have been free from all signs of the disease for the previous six months. Under certain conditions this rule might be relaxed ; thus, if the climate at the front is a good one, like that of South Africa, and the man had completed six months' energetic treatment without any fresh manifestation of the disease, he might be allowed to proceed, provided some arrangement existed by which treatment could be recommenced within three or four months. This might be managed by having one medical unit with each force equipped with the materials for injecting mercurial cream, and making the medical officer with the regimental unit responsible that the man attended.

Statistics of recent campaigns show that only a very small percentage of men are lost to the fighting strength of a force on account of syphilis, and it may be remarked that these figures refer to a period when the treatment of syphilis was not so thoroughly organized as it is now.

CHAPTER XII

GONORRHOEA

GONORRHOEA is a specific disease caused by the gonococcus, which usually invades the urethral mucous membrane during coitus. Before proceeding to discuss the treatment, a brief reference to the anatomy of the urethra, the general pathology and diagnosis of the disease, is required.

Anatomy.—For our present purpose the urethra consists of two portions, viz., all in front of the constrictor urethra, which is spoken of as the anterior urethra, while that beyond this muscle is called the posterior urethra, and is continuous with the bladder when full. Along the upper surface of the anterior urethra are Littré's glands and many lacunae which are especially numerous along the floor of the bulbous portion, while opening into the posterior are Cowper's glands, the ejaculatory and prostatic ducts.

Pathology.—The gonococcus was discovered in 1879 by Neisser. As seen in pathological secretions or in young cultures it is a diplococcus which is shaped like two coffee beans, or kidneys, with their flat, or concave, sides opposing one another, and the combined diplococcus is about the size of a staphylococcus. It is easily stained with any of the ordinary basic aniline dyes, such as methylene blue, carbol-thionin or carbol-fuchsin, and, an important point in its microscopical diagnosis, it is Gram-negative. To elicit this point the specimen should be treated as follows. A film of the suspected material is spread as thinly as possible on a slide and allowed to dry in

air. It is then fixed by passing it three times through the flame in the ordinary way and stained for one minute with aniline or carbol-gentian violet.[1]

The excess stain is removed with blotting paper and the specimen treated for one minute with Lugol's solution (iodine, 1; potassium iodide, 2; distilled water, 300); it is then dried with blotting paper and flooded repeatedly with absolute alcohol till a cloud of blue no longer rises on the addition of fresh alcohol. The last process should not take longer than two minutes, since some specimens of staphylococci are decolourized by longer application of alcohol. It is then counter-stained with Bismarck-brown or weak carbol-fuchsin (strong carbol-fuchsin, 1; distilled water, 19) washed with water, dried and examined. Gonococci stain brown or red, according to the counter-stain used.

The gonococcus will not grow on ordinary laboratory media and requires a medium to which fresh albumen has been added, human blood or serum, pleuritic or ascitic fluid being the best of these. As regards its resistance to external agencies, it is killed at once by drying, and at 40° C. it dies in six hours, however gradually the temperature is raised. It is not quite so sensitive to cold, though growth ceases below 30°C. It has been cultivated from infected towels and napkins which have been kept at room temperature for some hours, and Scholtz has cultivated it from infected bath-water after twenty-four hours. As regards the influence of chemicals, it is killed

[1] Aniline-gentian violet is conveniently made as follows :—

Add 3 c.c. of aniline oil to 100 c.c. of distilled water, shake well and filter through moist filter paper; to the filtered aniline oil water made in this way add 10 per cent. of a saturated alcoholic solution of gentian violet, shake well and filter on to the specimen. As aniline-gentian violet must be freshly prepared every week, it is more convenient, and equally effective, to use carbol-gentian violet, which keeps for weeks; this is made by adding 10 c.c. of a saturated alcoholic solution of gentian violet to 90 c.c. of $2\frac{1}{2}$ per cent. carbolic acid solution.

in ten minutes by 1 in 4,000 silver nitrate and 1 per cent. protargol; in 5 minutes by argentamin 1 in 1,000, and by oxycyanate of mercury 1 in 3,000, but is not destroyed in ten minutes by potassium permanganate 1 in 1,000, nor by zinc sulphate 1 in 400.

Until Finger published his investigations into the life history of the gonococcus within the urethra, the disease was looked on as an acute inflammation and treatment was accordingly directed to allaying this instead of attacking the gonococcus which causes the inflammation.

Finger showed that the gonococcus on gaining entrance to the urethra lodges on the mucous membrane and forms colonies; these multiply rapidly, producing fresh centres which spread over the surface of the urethra, till at the end of a week or ten days from the date of infection the whole urethra is involved up to the commencement of the bladder and at the same time every lacuna and duct opening into the urethra is invaded, their lining membranes being affected in the way about to be described. As the gonococci grow they produce extremely irritating toxins; these cause considerable inflammation of the mucous membrane with oedema and increased secretion which appears as a clear mucoid discharge; as the disease progresses serous exudation, mucus, pus and epithelial cells combine to produce the familiar creamy discharge. The serous exudation welling up between the epithelial cells opens up a path along which the gonococci grow to reach the sub-epithelial layer; in this position they are to a very great extent protected from the action of any medicament introduced into the urethra; obviously, therefore, if we can begin treatment before the gonococcus has gained a sheltered position, our task is much simplified; even if the gonococcus has penetrated the epithelial layer a vigorous attack may dislodge it, whereas if we adopt passive treatment and allow the germ to establish itself in the sub-

epithelial layer of the urethra and ducts opening into it, the task of ejecting it becomes very much more difficult and indeed in some cases almost impossible.

During the early stages alcohol increases the oedema of the mucous membrane and so facilitates the passage of the gonococcus to the deeper layers, hence its extremely harmful influence on the disease. Active treatment by washing away the superficial gonococci and their toxins cuts short the acute stage of the disease. When the process of cure commences the gonococci from the deeper layers are carried to the surface in the serous exudation. Irrigation increases this exudation and at the same time removes the germs and their products. It is, however, very doubtful if any irrigation or injection will effectively penetrate the ducts opening into the urethra.

Gleet, i.e. chronic gonorrhoeal discharge, shows that gonococci are still present and living somewhere in the urinary tract, most probably in the prostatic ducts or in one of the other ducts opening into the urethra or even in the subepithelial layer of the urethra. Alcoholic excess or sexual indulgence excites these foci to fresh activity, and the disease may again assume the acute form. If the focus is situated underneath the urethral epithelium the consequent inflammation leads to the formation of fibrous tissue, soft at first, which is called a soft infiltration; later on this tissue contracts and a stricture is formed.

An important point to bear in mind is that gonococci which have become quiescent, i.e. which have ceased to cause any signs of gonorrhoea in a male, may if deposited in the healthy vagina of a female give rise to an acute attack of gonorrhoea and in doing so regain their virulence; if the same person repeats the act of sexual connexion he may contract a fresh acute gonorrhoea, being infected with gonococci originally derived from himself.

Diagnosis. Symptoms, Discharge. — *Early cases.* —When the disease comes under observation at an early stage, say three or four days after infection, the lips of the meatus tend to stick together and a bead of mucoid discharge can be expressed from the urethra ; the man usually complains of some tickling in the urethra but no definite pain.

Acute cases.—It is at this stage of the disease that the man usually presents himself for treatment. The urethral discharge is thick and yellow, and micturition is extremely painful.

Sub-acute cases.—When the disease has progressed beyond the acute stage and is passing into the chronic one, there is a variable amount of watery discharge, and micturition is not attended by discomfort.

Chronic cases (Gleet).—When the disease has reached the chronic stage there is usually a bead of clear discharge when the man gets up in the morning, sometimes this may continue all day ; there is no pain on passing water.

Microscopic Examination of the Discharge.—In every case of gonorrhoea coming under treatment for the first time the discharge should always be examined microscopically in order to confirm the diagnosis and to obtain further evidence as to the stage which the disease has reached. For this purpose a minute bead of the discharge is spread out on a cover glass or slide and a smear preparation made just as in the case of a blood film ; when the discharge is very scanty care must be taken not to press the glass on to the glans penis and to obtain only secretion from the urethra and not from the prepuce, as the discharge of balanitis simulates that of gonorrhoea and often contains Gram-negative cocci. It may even be necessary to pass a loop of platinum wire into the urethra in order to obtain a specimen of the discharge. When there is no visible secretion but gonorrhoea is suspected, the man should be made to pass water into a urine glass. After stand-

ing for some time any mucus or sediment present is to be centrifuged and the deposit stained for gonococci, or the special method described below should be employed.

Staining.—For ordinary routine staining of gonorrhoeal pus, a saturated watery solution of methylene blue is the best stain. When the gonococci are relatively scarce, or, if greater accuracy is required, Gram's method should be employed, the gonococcus being Gram-negative. No staining method can be absolutely relied on to prove the absence of the gonococcus, and if this point is of very great importance, cultivation must be resorted to ; this is, however, troublesome and not practicable for the ordinary surgeon.

Early cases.—The discharge from these cases, when examined microscopically, is found to consist of epithelial cells, very few or no pus cells and quantities of gonococci, the pairs lying scattered all over the field. The prognosis in these cases is good.

Acute cases.—In these the pus cells are abundant, occupying the whole field. The gonococci are mostly found in circular groups within the leucocytes ; very few pairs are found free. In some cases the leucocyte has disappeared, leaving the group apparently free ; epithelial cells are few in number.

Sub-acute cases.—Pus and epithelial cells are the principal constituents ; the gonococci are few in number and lie free, no longer in groups.

Chronic cases and threads.—In the gleety discharge, threads and sediment obtained from the urine we find mucus the predominating characteristic, pus cells are numerous, epithelial cells less so, while the gonoccoci are very scarce, indeed a prolonged search may be necessary in order to detect a single pair.

The Laboratory Diagnosis of Chronic Gonorrhoea.—In old-standing cases of gonorrhoea, when the discharge is scanty and possibly intermittent, the diagnosis may cause

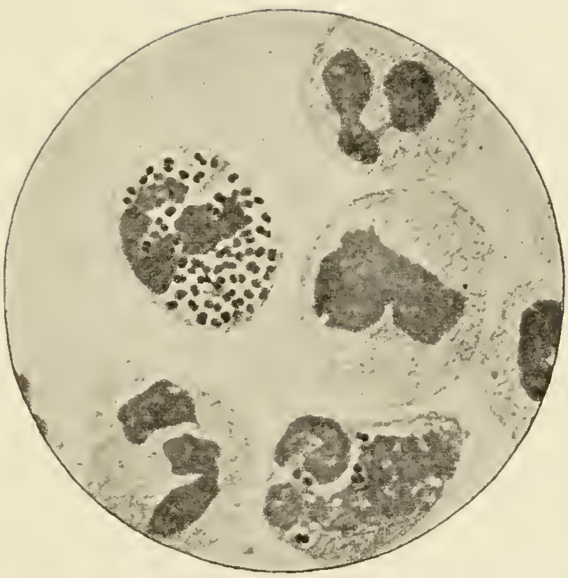


Plate XIV.—Micro-photograph of urethral discharge from a case of acute gonorrhœa. (Muir and Ritchie.)

[To face p. 234.

considerable difficulty. It is just in these cases, however, that laboratory methods are most required, since clinically it is impossible to say whether the patient is still suffering from gonorrhoea or only from post-gonorrhoeal catarrh.

Of many methods which have been devised with the object of bringing to the meatus any gonococci which may be lurking in or about the urethra the following may be mentioned: irritation of the urethra with chemicals, such as the injection of 1 in 2,000 perchloride of mercury or ½ to 1 per cent. silver nitrate; irritation by passage of bougies or dilators, combined possibly with massage of the urethra over the instrument; indirect irritation by administering beer or spices, or by means of sexual intercourse, with the use of a condom; massage of the urethra, prostate, seminal vesicles and Cowper's glands; injection of 3 to 6 per cent. perhydrol, with the object of carrying the gonococci to the meatus mechanically.

The following plan works well: If any discharge can be obtained from the urethra in the ordinary way it is stained by Gram's method and examined. The patient is then made to urinate into a glass vessel; if the urine is turbid with phosphates it is cleared with acetic acid; any threads which are seen are fished out and spread on a microscope slide. The following method of doing this is very successful. As much of the fluid as possible transferred with the thread is removed with blotting-paper, and the slide is then placed in a sloping position to allow one end of the thread to dry and fix it to the slide. The thread is then spread out as evenly as possible with the end of another slide and stained. Failing the finding of any gonococci in a thread the urine is centrifugalized, the deposit is resuspended in physiological saline, and the mixture again spun. A film of the resulting deposit is then stained and examined.

Gonococci may or may not be found by this preliminary test; in any case it is well to proceed further to ascertain in which

part of the urethra gonococci are lurking. The urethra is washed out with physiological saline solution till the latter returns quite clear. A little saline solution is then injected into the bladder, and the prostate and seminal vesicles are thoroughly massaged. Some prostatic secretion generally appears at the meatus as a result of this and a specimen should be spread on a slide for examination. After the massage the patient passes into a urine glass the saline solution which was injected into his bladder, and this is then centrifugalized and the deposit examined for gonococci. If gonococci are found in either of the specimens obtained in this way it is legitimate to infer that the prostatic gland or seminal vesicles are infected.

At a subsequent sitting Cowper's glands and the anterior urethra are examined. The urethra is washed out as before and having massaged Cowper's glands the anterior urethra is washed out with saline solution, which is preserved and centrifugalized.

The anterior urethra is examined in the following manner: The urethra having been washed clean in the usual way, the glans penis is grasped between finger and thumb of the left hand, and the penis put on the stretch. Then, with the thumb of the right hand on the dorsum and the index and middle fingers pressing on the urethra below, the urethra is well massaged from the bulb forwards.

The above may seem very complicated and tedious. It certainly takes some little time, but the trouble is well repaid by the information it affords, especially in obscure cases. By dividing the urethra up into districts one gains much more exact information as to the locality of the infection, and can treat accordingly. If the authors of many vaunted cures of gonorrhoea were to test them by this method they would probably not be quite so complacent about their remedies.

Differential Diagnosis.—When a man presents himself

with a thick purulent discharge escaping from underneath a long inflamed foreskin, the question at once arises as to whether we are dealing with balanitis or gonorrhoea. A smear of gonorrhoeal pus will present the characters described under those of the acute case, while if the disease is not of a gonorrhoeal nature the film shows in addition to quantities of pus cells a large variety of other germs, the most noticeable among which are spirochetes and some large diplococci which might be mistaken for the gonococcus.

In a few cases, especially if instruments have been used without sufficient precautions, a purulent discharge will be found to contain staphylococci or streptococci.

A simple urethritis, that is, a purulent urethral discharge which does not contain any pyogenic germs, must be rare in soldiers, as after examining several hundred specimens from different cases only three instances of this were noted.

Examination of the Urine.—Inspection of the urine gives a fair idea of the extent to which the urethra is affected (a most important point in the treatment); and in chronic cases which have no discharge from the meatus, such as those admitted for epididymitis, examination of the urine will often enable us to determine the presence of a chronic gonorrhoea.

The examination is carried out by means of "Thompson's two glass test," as follows: Give the man two urine flasks—ordinary tumblers do well or, at a pinch, the large bottles in which drugs are supplied may be used—tell him to pass four to six ounces of urine into the first glass and his remaining urine into the second. Take hold of these glasses by their upper portions and look through them at a window. The first glass contains, in addition to the urine from the bladder, the washings of the anterior urethra, while the second one has the secretion from the posterior urethra. The first glass, therefore, gives some idea of the state of the anterior urethra, and the second one that of the posterior urethra. If possible,

the urine which is passed on first rising in the morning should be seen, as this contains the accumulated secretion of the night. Some plan of preventing exchanges of urine among men in military hospitals must be employed, for a man anxious to get out of hospital will by arrangement produce perfectly clear urine. The simplest plan is to make the men pass their water one at a time in front of the wardmaster, who then locks it up pending the medical officer's arrival. At late stages of the disease, when the secretion is scanty, the urine, if sufficiently dilute, will appear to be clear, a fact which the soldier soon learns. Before discharging a man, it is well to make him pass water in the presence of the medical officer himself, so that there may be no possibility of trickery.

One or two fallacies in the two glass test must be mentioned. A mild degree of posterior urethritis may simulate an anterior urethritis, as the small quantity of secretion in the posterior urethra is passed into the first glass, leaving the second one clear. Should this be suspected, the urethra is to be syringed out before applying the test, any turbidity present will then have come from the posterior urethra. In very acute cases of gonorrhoea, all the pus in the anterior urethra may not be washed out into the first glass and so cause a turbidity in the second one.

Phosphaturia will cause a turbidity which, however, clears up at once when a drop of acetic acid is added.

Bacilluria will cause a slight degree of cloudiness in the urine ; the microscope will reveal the true cause.

Many degrees of turbidity are met with, not only when the man first comes under observation, but also as the disease progresses and the result of the treatment becomes apparent. Some kind of note should be kept of the condition of the urine, as it forms one of the most important guides to treatment. We are therefore confronted with the problem of finding such simple terms as will convey to our minds what the condition

of the urine was when last seen. The following terms were used for five years and found to answer fairly well; they are therefore given as a suggestion.

Turbid.—Applied to a very opaque urine found in well-established acute cases.

Cloudy.—A urine sufficiently dense to prevent objects such as the window bars being distinguished when looked at through the urine; this is the condition most commonly found in gonorrhoeas of moderate severity.

Hazy.—A urine of such density as only to permit of window bars being indistinctly seen when looked at through the urine.

Clear.—Applied to any urine when the bulk of it is clear (there may be threads or mucus in its lowest portion).

In addition to the above terms which describe the general condition of the urine with sufficient accuracy, other terms are required to denote the varying conditions of mucus so frequently found in gonorrhoeal urine. The following have been used satisfactorily.

Mucus (abbreviation = M [1]). Used when mucus is present, but of no definite appearance or character; this means a catarrhal condition of some portion of the urethra resulting either from the irritation of the disease or from a too prolonged treatment.

Flocculent mucus (abbreviation = FM). This term is used to denote a urine which contains quantities of fine particles of mucus floating evenly distributed throughout the specimen like snowflakes or minute granules of boiled sago. This condition is usually found in the urine of a man in whom treatment has been suspended too soon, and is the first sign of a relapse.

Mucous cloud (abbreviation = MC). This term is applied to the well-defined rounded mass of semi-transparent mucus

[1] The abbreviations save writing, when recording the daily changes in the urine.

containing threads and generally found floating at the lower part of the glass like a miniature cumulus cloud. It occurs in chronic cases, rarely contains any gonococci and but few pus cells; probably it is derived from the prostate, it is very persistent.

Mucous deposit (abbreviation = MD).—This is a thick even layer of mucus and pus filling up the lowest portion of the glass. It is of frequent occurrence during hot weather and in these cases the disease is generally very resistant to treatment; if examined microscopically it is found to contain numerous pus cells, gonococci and phosphatic crystals.

Threads (also called floaters).—These are found in the chronic stages of the disease in clear or nearly clear urine, sometimes they subside to the bottom of the glass and are only seen when the urine is shaken up. The easiest way to obtain a specimen is by catching one in the point of a pipette and transferring it to a slide where the urine can be drained off. The true thread is a cast of one of the follicles opening into the urethra; coarser stringy particles of mucus are also found which are not true threads.

Endoscope and diagnostic bougie.—When a case of anterior urethritis has reached the chronic stage and fails to respond to treatment, the explanation is usually to be found in the existence of a chronic inflamed patch of mucous membrane, an inflamed follicle, a tiny ulcer or what the Germans call a "soft infiltration" or a definite stricture. The urethra is to be examined by means of the endoscope or diagnostic bougie. This bougie has an acorn-shaped head, the blunter end of which is attached to the stem, so that it will readily pass beyond an early narrowing of the urethra, but when being withdrawn the shoulder, on meeting any constriction, conveys a sense of resistance to the hand. By measuring the distance of this spot from the meatus, its position can be located; an ulcer or tender spot may be found in a similar way.

Two patterns of endoscope are used, those in which a light is reflected into the urethra and those in which the lamp is passed down the cannula. The first kind enable instruments to be used through the cannula, but do not give a very good illumination ; some of these are made to allow of the urethra being inflated in order to detect early infiltrations. If Valentine's pattern is used, the instrument must be passed into the urethra for its whole length before withdrawing the guard, the urethra is then to be dried out with a swab and the lamp passed. The urethra is viewed as the instrument is withdrawn ; it must never be passed into the urethra without the guard being in position. When seen through the endoscope, the normal urethra presents a pale pink to red rosette, the numerous rugae running towards the centre and completely obliterating the canal. In the condition called soft infiltration, only one or two deep grooves are visible, the mucous membrane looking smooth and tense ; when a definite stricture has formed, the canal remains patient. Infected follicles stand up like bright red rosebuds.

CHAPTER XIII

GENERAL MANAGEMENT—DRUGS—METHODS OF URETHRAL MEDICATION—VACCINE AND SERUM THERAPY

Treatment.—The question of treatment may be dealt with under the following headings—

(1) General management of the case ;

(2) Drugs ;

(3) Methods of urethral medication.

(4) Vaccine and serum therapy.

(1) General Management.—It is usually recommended to keep the patient in bed for the first week or so ; Finger does not endorse this advice ; as he says that a gonorrhoeal patient kept lying idle in a warm bed is very prone to suffer from nocturnal erections which have a most harmful influence on the disease ; he recommends gentle walking exercise, and keeping the man employed, provided his work does not demand much physical exertion.

Diet. This should be light and plain, milk being the principal constituent, the following articles should be forbidden : alcohol absolutely, all spices, rich dishes, coffee, asparagus, pickles and acid fruits.

The bowels are to be kept freely open : the urine should be rendered dilute and unirritating, for which purpose barley water in large quantities is to be given.

Hot baths are comforting and exercise a beneficial effect on the early stages of the disease.

The patient must be cautioned as to the danger of infect-

ing the conjunctivae. Some plan should be adopted to prevent the discharge from soiling the clothing; placing cotton wool under the foreskin is not sound, as it tends to retain the discharge. A better plan is to make a loosely fitting cover for the penis, with some absorbent material to project beyond the end of the penis and so absorb the discharge.

(2) Drugs.—These may be divided into (1) For internal use, and (2) for local use in the urethra.

The drugs which are supposed to have a specific action in gonorrhoea are: sandalwood oil, cubebs oil and balsam of copaiba; all of these are inclined to upset the digestion. Some of the newer preparations are much pleasanter to take and do not cause disturbance of the digestive tract. Gonosan is one of the most efficient as the active principles of several balsams have been combined in the formula, but we have not been able to satisfy ourselves that it exerts a specific effect on the disease. Less nauseating and probably more effective in the acute stage of the disease are urotropine, salol, salicylate of soda, boric acid and benzoate of ammonium or benzoic acid: the latter is especially indicated in cases which have the thick mucous deposit with phosphatic crystals. Fournier recommends full doses of the balsams during the stage of decline, but our experience with balsams in the treatment of gonorrhoea has not impressed us very favourably with their value; in fact, we very much doubt if any appreciable difference could be detected between two series of cases, one receiving full doses of balsams and the other none.

The remedies which have, at different times, been recommended for urethral injections during gonorrhoea are so numerous that only a few of the more recent ones, which have established a definite claim to consideration, will be noticed here.

Potassium permanganate.—This is cheap and in early cases a very effective drug. It can be used as an injection, $\frac{1}{8}$ gr. to the

ounce, or, as an irrigation, 1 gr. to the pint in early cases, and up to, but never exceeding, 2½ grs. to the pint in later cases. This drug is less irritating than any of the silver preparations, and provided the disease has not attained the chronic state, will nearly always yield good results.

The most powerful agent we have for killing the gonococcus is nitrate of silver; unfortunately this drug is very irritating to the mucous membrane (unless used in very dilute solutions), and it precipitates in the presence of the sodium chloride in the urine, losing much of its therapeutic value. The newer silver preparations (combinations of nitrate of silver with organic substances) are very effective in destroying the gonococcus and are without the disadvantages of nitrate of silver. The best known of these salts are protargol, albargin, icthargan, argonin, largin, argentamine and argyrol.

Protargol.—This salt is generally used for injections. Neisser recommends beginning with a solution of 1 gr. to the ounce and gradually increasing this up to 4 or even 8 grs. to the ounce. It can also be used for irrigating the urethra, 10 to 20 grs. being used to the pint of water. It is to be dissolved in cold distilled water. If hot water is used, the salt is liable to break up and become inert.

Argyrol contains a very large percentage of nitrate of silver and can be used for injections in strengths of 5 to 20 per cent.; it has been very well spoken of, but its cost is prohibitive for army purposes.

Albargin and icthargan are mostly employed for irrigations, 2½ to 5 grs. being used to a pint of water. They are specially indicated when the acute stage has passed off, but may be used at any time, if they cause the patient no discomfort. They are very much more expensive than the permanganate; hence for economical reasons it is well to begin with the permanganate and keep the expensive silver salt in reserve till the permanganate has had a fair trial.

Nitrate of silver.—This salt has been used as an injection in very early cases in 1 to 2 per cent. solutions with the idea of aborting the disease; the treatment is, however, very painful and the results are uncertain. One to $2\frac{1}{2}$ grs. to the pint of water forms a useful solution for the irrigation of chronic cases. It is also used in 1 to 2 per cent. solutions for the treatment of local lesions in the urethra, being applied by means of Guyon's syringe.

The other silver salts do not seem to have held their position as medicaments. A few other drugs may be mentioned, such as picric acid; this was recommended as an injection, 1 to 2 grs. to the ounce being used; it has been reported to cause excessive secretion. Formalin 2 to 5 minims to the ounce, and icthyol in 1 to 2 per cent. solution, have also been well spoken of.

To deal with the catarrh which sometimes remains after the gonorrhoea has been cured, astringent injections are employed. A few formulae are given in Appendix VII.

Methods of Urethral Medication.—These may be roughly classified as (1) small syringe, (2) large syringe, (3) irrigation, (4) jellies, etc., (5) by the application of heat, (6) by means of instruments, (7) ionization.

(1) *Small Syringe Method.*—The syringe should have a blunt cone-shaped nozzle, so as not to penetrate the urethra, and a capacity of $\frac{1}{3}$ to $\frac{1}{2}$ oz. It should be disinfected each time after use. For *anterior urethritis* Neisser and Finger both favour this method, using protargol. They, however, strongly insist on the following points being observed: (*a*) The injection must be of sufficient volume to gently distend the mucous membrane, and thus allow the solution to get into contact with every portion of its surface; about one-third of an ounce is the quantity usually required. (*b*) The injection must be retained for some time; Finger directs that *each* injection be held for two minutes on the first day,

three on the second, increasing the time daily up to fifteen minutes. (*c*) At least three injections should be given daily, at intervals of eight hours, say at 6 a.m., 2 p.m., and 10 p.m. (*d*) The strength of the solution should be as much as the patient can tolerate.

(2) *The Large Syringe Method.*—This method may be used for either anterior or posterior urethritis. It is somewhat tiring for the medical officer, and soils his hands, but gives good results. A four or six-ounce metal syringe (an ordinary ear syringe answers fairly well) to which a blunt rubber nozzle is attached, is filled with solution selected. With his left hand the surgeon seizes the man's glans, while with the right he presses the nozzle of the syringe into the meatus. With a short, sharp push the urethra is fully distended, and the fluid immediately allowed to escape by withdrawing the syringe. This is repeated till the syringe is empty. Should it be desirable to inject the bladder, first wash out the anterior urethra, then refill the syringe, and maintain steady pressure till the sphincter yields, allowing the fluid to run into the bladder. After a few minutes the man should be told to empty his bladder into a glass vessel, and show this to the surgeon.

(3) *Irrigation Method.*—Apparatus required: An irrigator can, or better, hanging glass vessel, with five feet of rubber tubing, a push stop-cock, and a Maiocchi's double-channel glass nozzle. The irrigator should be five feet above the man's penis; when the anterior urethra is being irrigated, reduced pressure may be used by only opening the stop-cock half-way, or if no stop-cock is employed the rubber tube may be partially compressed by the fingers, while if it is desirable to fill the bladder, the tap should be fully opened. In acute cases the best and cheapest solution to use is potassium permanganate, beginning with 1 grain to the pint and never exceeding 2½ grains to the pint. The solution should be about body temperature, and the irrigation employed each morning,

or, if no discomfort is experienced by the patient, a second irrigation may be given in the evening.

To apply this treatment the surgeon, wearing a mackintosh apron, should be seated opposite to the patient, and the latter's penis pulled through a hole in a piece of waterproof reaching down to a slop bucket. Turn on the tap, and wash the glans thoroughly, then, keeping the tap open, slowly apply the nozzle to the meatus, and, increasing the pressure by opening the tap a little more, allow a pint of fluid to run through. The fluid will run up to the sphincter, but usually not beyond as long as the outflow tube is left open; if it is desired to fill the bladder, close the escape tube by pressing the finger on it, and tell the patient to try to pass his water; this relaxes the sphincter and allows the fluid to flow into the bladder. When the man feels that his bladder is full, shut off the stream, and let him empty his bladder into a glass vessel. Note how much he can hold comfortably, and whether the solution shows much change as the result of having been in his bladder. The irrigation (as also the large syringe injection) thoroughly washes out the urethra, carrying away all gonococci lying on the surface and in the folds of the mucous membrane. It also has the effect of massaging the epithelium, which subsequently sets up a certain amount of oedema and serous exudation in which the deeper-lying gonococci are carried to the surface. Occasionally, marked oedema of the penis may occur; this will subside if left alone. Irrigation may be employed at any stage of the disease, and is not contraindicated by epididymitis.

(4) *Jellies, bougies.*—The silver salts may be made up in the form of jellies or bougies; in this form the drug is retained in contact with the urethral mucous membrane for a longer time than is possible when watery solutions are used. This form of medication should not be employed till the sub-acute or chronic stage has been reached.

Schindler's jelly is made up as follows :—

Agar Jelly 2·5 per cent. . . . . . 40 parts.

Melt and add

Distilled water . . . . 160 parts.

When cold incorporate by rubbing

Protargol . . . . 1 part.

Leistikow's bougies have a basis consisting of starch, sugar, dextrine and a little glycerine. A silver salt is added and the mass is rolled into bougies. Before being used they are dipped into hot water, which makes the outside smooth and slippery. When left in the urethra they slowly dissolve.

(5) *The Local Application of Heat.*—The theoretical foundation of this is the destructive effect of comparatively low temperatures on the gonococcus, which dies in six hours at 104°F. and at higher temperatures in a considerably shorter time. This weak point in the gonococcus has long been recognized, and many have advocated the treatment of gonorrhœa with hot sitz-baths. Few, however, have ventured to apply heat more directly to the urethra, fearing, probably, that the necessary instrumentation would result in epididymitis and other complications. Kyaw (1912) reported considerable success with diathermy, but the necessary apparatus is too costly to permit of the general application of this form of treatment. The same worker subsequently treated a number of cases successfully with a bougie through which hot water circulated. Lieut. Harold at Rochester Row treated some cases by gradually raising the temperature of the irrigating fluid to 120° F., but with only partial success. For some years Dr. Valentine of Silchar, India, has treated gonorrhœa successfully with the hot-water bougies described below, and his apparatus has recently been used at Rochester Row by Major G. J. Houghton, to whom he suggested it. The writer has used an electrically-heated bougie devised for the treatment of stricture by Dr. Ph. Kobelt.

The experience of this form of treatment has so far been so favourable at Rochester Row that the technique of its application may be given in some detail.

Valentine's hot-water bougie.—This is a silver catheter (No. 9 or 10 English) which is closed at its distal end ; into it is passed to within an inch or so from its distal end a No. 2 catheter, which projects about an inch from the proximal end of the enclosing catheter. Here the two are soldered together so as to form a water-tight union, and a short lateral tube is soldered into the outer catheter, also at its proximal end, to lead away the water.

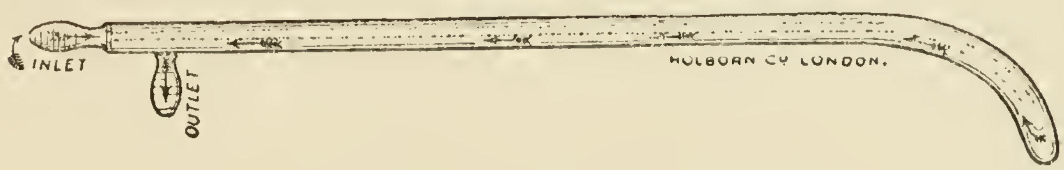


FIG. 14.—Valentine's water-heated bougie.

The instrument is used in the following manner. An atropine suppository (gr. $\frac{1}{75}$) is administered to the patient the night before and again on the same morning. Immediately before the bougie is passed his urethra is irrigated in the usual manner. He then lies on a couch and is adequately protected with a waterproof sheet. The sterilized and lubricated bougie is connected by its inner tube to a rubber tube leading from an irrigator vessel, which is filled with water at 114° F. and placed about 18 inches above the couch. This rubber tube is provided with a clip. To the lateral tube is attached another short rubber tube to lead away the water to a conveniently placed bucket.

The bougie is then passed into the bladder and the clip opened to allow the water to flow from the irrigator down the inner tube of the bougie and back by the outer tube to the outlet. The temperature of the water in the irrigator is gradually raised to 125° F. by adding more hot water to it, and at

this temperature the water is allowed to flow through the bougie for 25–30 minutes.

Kobelt's electrically heated bougies.—These are gum-elastic or metal bougies which are heated by means of an electric

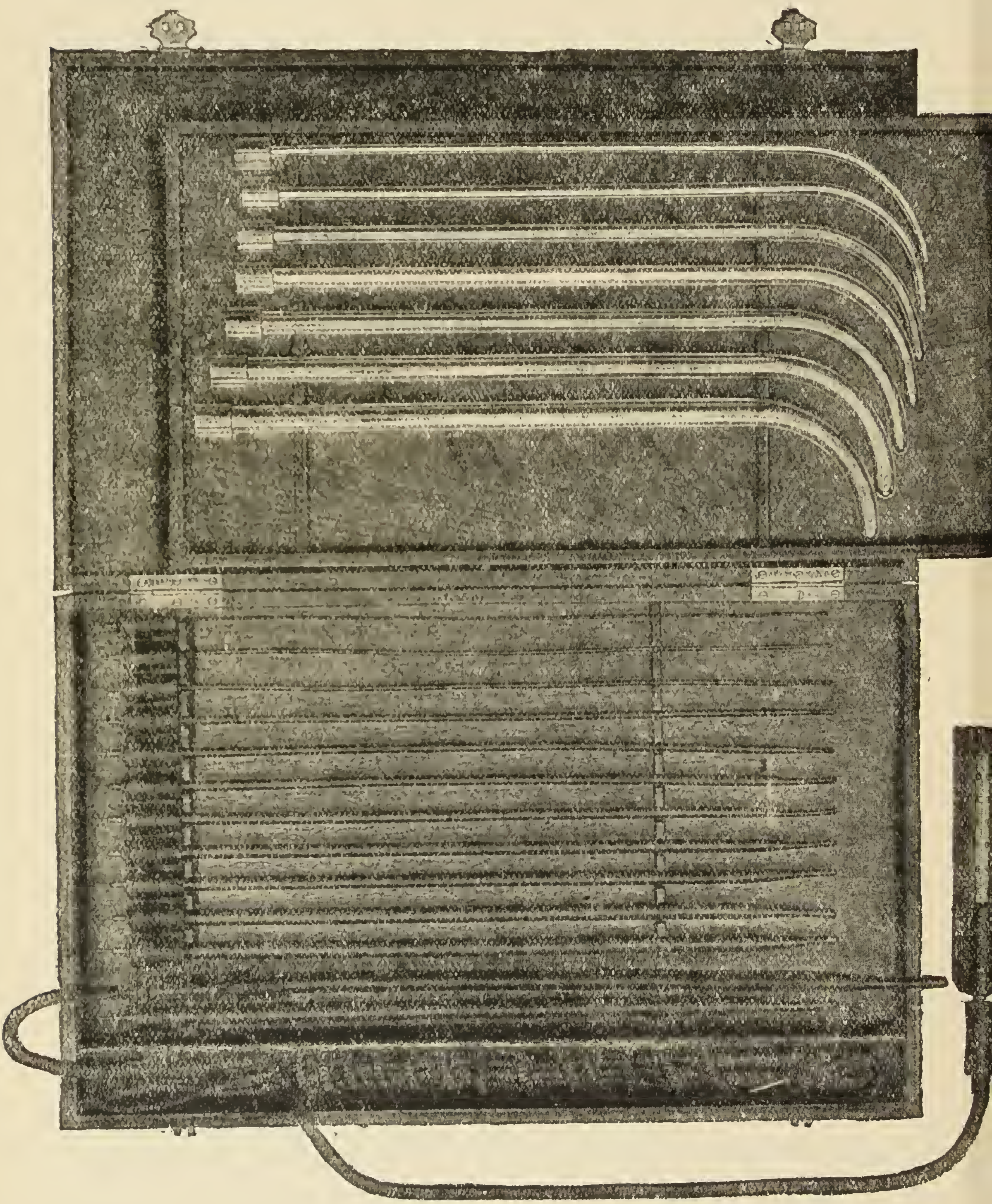


Fig. 15.—Kobelt's electrically heated bougies.

resistance coil enclosed within them. In the circuit between bougie and source of electricity is another resistance coil in which is inserted the bulb of a thermometer which records the temperature of the heater. The source of electricity is either an accumulator such as is used for urethroscopic examination or the main supply suitably converted.[1]

The patient having been prepared with atropine and his urethra irrigated as described above, the bougie is passed into the bladder. The current is then turned on and the temperature regulated through the resistance at the electrical source. The writer has found that with a No. 14 (French) gum-elastic bougie it is easy to raise the temperature till the thermometer registers 180° F. without any harm resulting. This temperature is maintained for 15 minutes, and altogether the bougie is within the urethra for 30–35 minutes. Theoretically such a temperature is dangerous to the tissues, but probably the heat is dissipated so quickly that the temperature outside the bougie within the urethra never approaches that of the electric heater as registered by the thermometer. Whatever the explanation, if the temperature is raised gradually the patient makes no complaint, and the secretion microscopically examined immediately after removing the bougie does not appear to have been heated unduly.

With either form of apparatus the best results have followed the application of the bougie two or three times a week rather than more frequently.

The results both in acute and subacute or chronic cases have, so far, been very promising. Out of 16 acute cases treated in this way, in 11 gonococci could not be found later than the 5th day. In the remaining 5 they disappeared on the 7th, 9th, 11th, 13th, and 18th days respectively. In six other

[1] Kobelt's bougies can be obtained from Reiniger, Gebbert and Schall, Erlangen-Berlin, or from Messrs. Schall & Son, 71 and 75, New Cavendish Street, London, W.

acute cases they were still to be found, though scanty, at the time of writing, on the 7th, 9th, 10th, 13th (2) and 18th days. Out of 13 subacute or chronic cases gonococci could not be found later than the 3rd day in 7, nor later than the 9th day in the remainder. The discharge sometimes ceases very quickly, but generally it changes to muco-purulent, then sero-mucous, and so persists for a week or two longer. As regards the risk of complications which might naturally be expected under such treatment, out of 35 cases 2 have suffered from mild epididymitis. On the other hand, a patient with sub-acute epididymitis on admission showed very marked improvement on the day after the first application of the treatment. Such local complications as periurethral infiltration or abscess rapidly improve, and the condition of the prostate throughout is much more frequently normal than is usual with cases of gonorrhœa treated by other methods.

Of the 22 acute cases mentioned above, 10 were discharged to duty after an average of 15·8 days from commencing the treatment, and 12 were still in hospital at the time of writing after an average of 14·8 days. Of the 13 chronic cases 11 were discharged to duty after an average of 14·5 days from commencing the treatment, and 2 remained in hospital after 15 and 11 days respectively. Out of the 21 patients discharged to duty 3 returned with a slight purulent discharge, but in 2 of these no gonococci could be found after several examinations.

The treatment is, of course, in its infancy, and quite possibly better results will follow as the technique improves. It is probable that besides the immediately destructive effect of the heat on the gonococci this treatment induces similar conditions to those obtained by Bier's congestion treatment of the urethra. If this is so then the use of gonococcal vaccine in conjunction should be beneficial. Sufficient observations have not been made to justify any definite conclusion on this point, but results obtained so far support such a belief.

(6) *By means of instruments.*—For chronic cases, in which the above plans have failed to obtain a cure, one of the following is to be tried—

Bougie.—Passing a large bougie sometimes has an excellent effect on a chronic case, although it is not quite clear why this should be so, for any instrument which will pass through the meatus is not large enough to stretch the urethral mucous membrane.

Dilators.—The expanding dilators are made of such a size that, when closed, they will pass through any ordinary meatus, but when in the urethra can be expanded, so as to thoroughly stretch the mucous membrane. Kollmann's pattern is designed to allow of flushing the canal with the dilator expanded and in position.

Guyon's and Ultzmann's instillations.—Both of these plans consist in introducing a few drops of a strong solution of nitrate of silver into the urethra at the site of any inflamed patch. In both a syringe and catheter are used, the eye of the catheter is brought as nearly as possible over the spot and, by means of a screw piston, one or two drops of the solution are allowed to escape. The apparatus may be improvised by using a fine soft catheter and a hypodermic syringe.

Endoscopic medication.—When the endoscope reveals an inflamed patch, local applications may be made by means of a swab through the cannula of the instrument. Text-books also describe the destruction of inflamed follicles by means of the electric cautery or slitting these up with a specially designed knife.

Prostatic massage.—When the gonococcus has succeeded in establishing itself in the prostatic ducts, the only possible way of getting rid of it from this situation is by massaging the prostate. This can be done by inserting the finger into the rectum and expressing the contents of the prostatic follicles; the bladder should first be filled with some antiseptic solution.

An electric masseur has been invented for this purpose, but beyond being cleaner it is doubtful if it offers any advantage. Before massaging the prostate it is advisable to employ suppositories of atropine to prevent the occurrence of backward currents in the vas ; these are set up by mechanical irritation of the caput gallinaginis and may carry the infection to the epididymis. The suppositories should be made up to contain $\frac{1}{75}$ of a grain of atropine in each ; one should be given on the night before and a second on the morning before the massage is carried out.

(7) *Ionization.*—The results of ionization with zinc in chronic cases are distinctly encouraging. A special electrode of pure zinc in the form of a stylet is enclosed in a gum elastic catheter and attached to the positive pole of a battery. Some zinc sulphate solution $\frac{1}{4}$ per cent. strength is injected into the bladder and the sheathed stylet passed into the urethra ; the end of the catheter prevents the solution from escaping. The circuit is completed and a current of 5 milliamperes passed for five minutes. This treatment induces a purulent urethral discharge which lasts for a few days.

The Vaccine and Serum Therapy of Gonococcal Infections.—Like many other bacterial infections those produced by the gonococcus are often favourably influenced by injections of dead cultures of the specific micro-organisms.

It is chiefly in epididymitis and such gonococcal metastases as arthritis, teno-synovitis, iritis and sclerotitis that most benefit has followed the specific vaccine. Sometimes the effect of this is almost magical, a marked improvement being noticed on the following day and a few injections sufficing to effect the patient's recovery. In other cases vaccine appears to act more slowly, but most workers agree that in the great majority of the complications of gonorrhoea it has a beneficial influence.

With regard to gonorrhoeal urethritis and mucous membrane

affections there is by no means the same agreement. The majority consider it of little or no value in gonorrhoea of men; but some workers, notably Hamilton and Cook and Butler and Long, have reported excellent results from its use in the vulvo-vaginitis of little girls, while other workers have reported favourably on its use in the gonorrhoea of women. Allen and Eyre and Stewart recommend the use of vaccine in ordinary gonorrhoea, and Simon, writing on the effect of arthigon, a commercial gonococcal vaccine, though he expresses disbelief in its effect on urethritis, mentions two cases of epididymitis in which the posterior urethritis cleared up under its use.

The adverse opinions seem to be based on grounds which are inconsistent. If gonococcal vaccine is useful in the treatment of gonococcal metastases, presumably it acts by improving the patient's resistance to the gonococcus. If, therefore, the effect of injecting vaccine is to improve the resistance, it should be useful in preventing or nipping in the bud the complications of gonorrhoea. This alone should justify its use.

Further, as the gonococcus penetrates deeper and deeper into the urethral mucous membrane, it approaches more nearly the blood vessels in which, after suitable gonococcal vaccination, there should be circulating gonococcal antibodies and *ipso facto* an antagonistic medium. On this ground the gonococcal urethritis of a patient who is treated with vaccine should be more superficial.

Lastly, gonococcal vaccine or any other treatment of gonorrhoea cannot fairly be judged by the standard of cure which seems to be adopted by many who have written on this subject. To assume that gonorrhoea begins and ends with urethral discharge is to take altogether too narrow a view of the question. After all, urethral secretion manifests the effort of the tissues to cast out the invader; when it ceases it does

not necessarily indicate that the fight has been successful as far as the tissues are concerned. More often it means, as Lieut. Harold and the writer found in a series of observations made at Rochester Row, that the tissues have become tolerant of the gonococcus. In a series of cases in which a search was made for gonococci in the prostatic secretion long after all discharge had ceased under purely local treatment, gonococci were found every time.

Judged by the presence or absence of gonococci in the urethra or ducts which open on the urethra, the treatment of gonorrhoea with the assistance of vaccine gave results which, if far from perfect, were very much superior to those attained by the use of local treatment only or supplemented with balsams. Three series of cases were treated at the same time: (*a*) with local applications, (*b*) with vaccines only, and (*c*) locally and with gonococcal vaccine. It was found that under local treatment only and with local treatment plus vaccine, the discharge took about the same time to clear up, but that whereas under purely local treatment gonococci could easily be demonstrated when the patient was apparently cured, under vaccine and local treatment it frequently happened that gonococci could not be demonstrated in the prostatic or any secretion which could be expressed from the anterior urethra.

Gonococcal vaccine cannot, however, replace local treatment, if we may judge from the results of the above series, since patients treated only with vaccine made very poor progress.

After the patient is fit for discharge from hospital we have found it useful to continue the injections of vaccine weekly for about six weeks, having by this means very considerably reduced the number of readmissions for relapse.

In the treatment of chronic gonorrhoeal urethritis, where the gonococci are safely established in the follicles and gland

ducts which open on the urethra, the chances of purely local treatment succeeding in removing the micro-organisms seem about as small as those of clearing out a room by washing down the passage outside it, and our only means of attacking them is by raising the patient's resistance. It is true that vaccine may fail also, but it often succeeds where purely local measures have failed entirely.

Regarding the effect of vaccine in preventing complications, in 200 cases which were treated throughout with vaccine at Rochester Row only two cases of gonococcal metastasis occurred. One was a very mild case of teno-synovitis of the wrist in a signaller, and the other, a more severe case of teno-synovitis of the wrist and hand under vaccine treatment. Both recovered with perfect movement.

The prevention of epididymitis is another matter. Here the complication occurs by extension along a mucous membrane and it is admitted that the influence of antibodies cannot be brought to bear so directly. In two parallel series of 43 cases each treated at Rochester Row the incidence of epididymitis amongst the vaccine cases was less than half that which occurred in those treated identically but without vaccine.

Gonococcal vaccine may be prepared locally or purchased from any of the institutes which prepare vaccines and sera for the market.

If prepared locally it would be ideal to use the patient's own strain, but the gonococcus is rather more difficult to grow and standardize than most other organisms, so that a stock vaccine made from eight to a dozen strains is generally used in routine work.

I have almost always used vaccine which was prepared locally, but have occasionally treated patients with arthigon, a commercial vaccine, prepared according to Brück's directions, which seems to be very popular on the Continent. The results appear to have been very similar.

In preparing gonococcal vaccine it is better to grow the gonococcus on serum, pleuritic, or ascitic agar, rather than on blood agar, since the débris in the latter makes the counting of the cocci very difficult. The vaccine may be standardized by Wright's method or in a haemocytometer, according to the directions of L. Murray. After counting it may be killed by heat, but I think that this interferes with its immunizing power and prefer to kill it with 0·5 per cent. carbolic acid.

The dosage of gonococcal vaccine varies very considerably with its source and method of preparation, as well as with the type of gonococcal infection for which it is intended. If prepared from cultures which were isolated many months previously and sterilized by heat, very much larger doses can, and must be, given than when recently isolated and killed with a weak antiseptic. This probably explains the great difference of opinion which prevails as to the correct dose to administer. Some workers, e.g. Eyre and Stewart, who use recently isolated cultures, recommend very small doses, 500,000 to 2·5 or 5 millions and never exceed 25 millions; others who use older strains give 50 millions at first and may increase to 1,000 millions. Continental workers who use arthigon give 0·5 c.c. to 2 c.c., arthigon being supposed to contain 20 millions per c.c., though it looks much stronger than this. I have found it necessary to find out by cautious trial the best initial dose of each batch of vaccine prepared. It would afford some guide if the makers of commercial vaccines would give some information as to the age of the strain and the method of preparation of their vaccine.

Generally speaking, in acute cases of gonorrhoea or any of its complications the smallest dose of the vaccine should be given, taking account of the above considerations, and the greatest caution should be exercised about increasing the dose; for example, of the vaccine I am at present using I commence with 2·5 millions, and if this is not followed by

marked local and general disturbance, the dose is increased to 5 millions three to four days later. This dose is not exceeded and is injected twice weekly throughout the acute stage.

When the acute symptoms have subsided, and the discharge has practically ceased in gonorrhoea, or the pain is slight and limited to one or two joints in arthritis, the dose is increased to 10 millions, then 20, and so on gradually up to 30, 100, or even 200 millions, the succeeding dose being raised if the preceding one caused no marked increase of symptoms. When 20 millions or over are given, the injection is made weekly instead of bi-weekly, as in the case of smaller doses.

In acute arthritis absolute rest to the affected joints is very necessary, since apart from loss of rest caused by the pain of unfixed joints it is very possible that the patient may receive excessive doses of gonococci and their toxins by auto-inoculation.

In chronic cases of gonorrhoea I have had the greatest success from pushing the vaccine to the extent of producing a urethral discharge.

Serum Treatment.—Rogers and Torrey have claimed good results from the treatment of cases of epididymitis, arthritis and other complications of gonorrhoea with the serum of rams which had been immunized against many strains of gonococci. The serum was injected on alternate days or at longer intervals in doses of 2 c.c. to 6 c.c. according to the reaction which followed each injection. In a few cases symptoms of serum sickness followed and some of these were very severe. The serum does not seem to have any good effect in urethritis. A serum sold by Burroughs, Wellcome & Co. is given in larger doses, and excellent results are reported by some workers with it. It must be remembered that most anti-diphtheritic serum is prepared from horses and it would be well to avoid the risk of sensitizing to horse serum a patient who at any time later might contract diphtheria and have to be dosed with diphtheria antitoxin.

CHAPTER XIV

CHOICE OF METHODS AND DRUGS—COMPLICATIONS—TEST OF CURE—WOMEN AND CHILDREN

Selection of Method and Drug.—Having determined the extent of the urethra affected and the stage of inflammation which the disease has reached, the surgeon has to decide with what drug, and by what method, he will attack the gonococcus. Experience will soon lead him to adopt one or other method, but for the guidance of those who have not had much to do with the treatment of gonorrhoea, the various conditions likely to be met with are enumerated below, with treatment suitable to each. It may be remarked here that the treatment of many cases of gonorrhoea is most disappointing, and that the surgeon will occasionally almost despair of ever effecting a cure in certain obstinate cases.

Anterior Urethritis.—*Early acute* cases in which the discharge has not yet become definitely purulent, should be given injections of gonococcal vaccine to increase the patients' resisting powers and so prevent the gonococci from penetrating the deeper layers of the mucous membrane. The local treatment may be carried out by means of :—

(1) Injections.—Begin with one grain of protargol to the ounce and increase the strength daily till 4 or even 8 grs. to the ounce is being used, the increase is to be made according to the patient's sensations when the injection is being made; thus if there is no pain the strength can be increased, but the man should never suffer acute pain as the result of the injec-

tion. The injection is to be made at least three, or, better, four times in the day and each injection is to be held as long as the patient can bear it.

(2) Large syringe.—The anterior urethra can be washed out by means of the large syringe at least twice daily, using potassium permanganate 1 gr. to the pint.

(3) Irrigation.—Half to one pint of a solution of 1 gr. to the pint of potassium permanganate may be used as an irrigation in the morning, or again in the evening, or even three times in the day, if the patient experiences no discomfort. An irrigation in the morning, followed by one or two injections in the evening, often acts very well. When dealing with soldiers, the irrigation treatment yields better results than either of the syringe plans.

Acute stage (with purulent discharge and turbid urine in the first glass). In these cases injections of gonococcal vaccine should be employed, as there is considerable evidence to show that their effect is to reduce the likelihood of extensions to neighbouring parts. The ordinary case of gonorrhoea may be treated as detailed under the early acute stage. Occasionally one meets with an excessively acute form in which the discharge is profuse and possibly blood-stained, the penis is swollen, the man looks decidedly ill and complains of intense pain on attempting to pass water. In such a case it is hardly wise to apply any treatment which involves much mechanical disturbance of the urethral mucous membrane; any local treatment employed should be merely for the purpose of facilitating the escape of the pus, for example, injections of warm water or weak permanganate solution given very gently and only penetrating a short way into the urethra. The treatment should be restricted to injections of gonococcal vaccine and to making the urine as unirritating as possible by giving large quantities of fluid to drink, together with alkalies, infusion of buchu, etc. Morphia suppositories relieve the pain

to a great extent. Hot hip baths also have a beneficial effect. Ice bags may be applied to the penis. Should retention occur, a full injection of morphia into the perineum with the addition of adrenalin, and followed by a hot bath, may succeed in reducing the swelling sufficiently to permit of the bladder being emptied. If a catheter has to be passed, and this should if possible be avoided, a urethral injection of a 10 per cent. solution of cocaine with a few drops of adrenalin solution should be given a quarter of an hour before passing the instrument. In a day or two the intensity of the attack should have sufficiently diminished to permit of the ordinary treatment being resumed.

Sub-acute stage (in which the discharge is thin and watery, pain absent or slight, and the first glass only very slightly clouded). Injections of protargol beginning with 2 grains to the ounce, irrigations of potassium permanganate 2 grains to the pint, or better, irrigations with albargin beginning with 2½ grains to the pint and increasing to 5 grains to the pint. Good results have been obtained by irrigating the urethra three times a day with potassium permanganate solution 1 in 4,000, and after each irrigation using injections containing sulphate of zinc ½ grain, sulphate of copper ¼ grain, in an ounce of water. The large syringe if preferred may be used instead of the irrigation apparatus.

Chronic stage (with no pain on passing water, a gleety discharge and a clear urine containing a little mucus and threads).

Injections of protargol 4 to 8 grains to the ounce may be tried; or irrigations with albargin 5 grains to the pint, or nitrate of silver 1 to 2 grains to the pint. Injections of Schindler's protargol jelly after irrigating with potassium permanganate solution will be found to give better results than the above plans. Ionization with zinc should be tried in chronic cases. These plans of treatment may be successful, but frequently something more will be required. If available the

endoscope should be employed, in order to determine what particular condition is keeping up the discharge. If an infected follicle is detected, one of the expanding dilators is to be used, or a large bougie passed, and immediately afterwards an injection or irrigation employed in order to wash away the gonococci which have been expressed. If the surgeon possesses the requisite means and skill, the follicle should be slit up or destroyed by means of the galvanic cautery. An ulcer if present should have a strong solution of silver nitrate (4 to 10 grains to the ounce) applied to it by means of one of the instillation plans. Soft infiltrations require stretching, preferably with the expanding dilator.

It should be remembered that a chronic mucoid discharge may be set up as the result of irritation, the irritation being a consequence of the disease or of a too prolonged treatment; if so definite threads are not likely to be found.

Posterior Urethritis.—(Both glasses show more or less turbid urine, the first usually more so than the second.)

When the whole urethra is affected the small syringe is useless, as the fluid injected does not reach the posterior portion, or if it does the quantity is quite insufficient to influence the course of the disease.

During the acute stage the urinary antiseptics, such as urotropine, should be given; when the sub-acute stage is reached the balsams are to be preferred; the active principles of all these drugs being excreted by the kidneys act on the gonococci while the urine lies in the bladder.

In all cases of posterior urethritis injections of gonococcal vaccine should be given to prevent extensions of the infection.

Acute stage.—Irrigations with potassium permanganate 1 to 1½ grains to the pint; the anterior urethra is always to be well flushed out first, then closing the out-flow fill the bladder as full as the man can comfortably bear. After a few minutes the man should empty his bladder into a glass vessel and show

the contents ; at first, while the disease is acute, the fluid returned has a turbid brown appearance ; as the disease subsides the fluid returns nearly in the condition in which it was introduced. The large syringe (Janet-Franck) may be used in the same way, first washing out the anterior urethra and then filling the bladder ; it is, however, a very tiring method for the medical officer if many cases have to be treated.

Sub-acute stage.—The same methods as above, using potassium permanganate 1½ or 2 grains to the pint, or better albargin 2½ to 5 grains to the pint. The other silver salts, such as icthargan in the same strength as albargin, or protargol 10 grains to the pint, may be used if desired.

Chronic stage.—The same methods as above, using albargin 5 grains to the pint, or nitrate of silver 2 grains to the pint, should be tried. If these fail after a fair trial, the prostate has probably become affected, and prostatic massage preceded by atropine suppositories should be employed immediately before or after filling the bladder with a solution of some preparation of silver nitrate.

Complications, Anatomical and Functional.—*Phimosis.*—A long foreskin, if inflamed and swollen, prevents proper treatment being carried out by making the meatus inaccessible. In these cases the disease is usually well established, hence it is wiser to try to reduce the inflammation sufficiently to expose the meatus rather than to slit up the foreskin ; a fresh wound exposed to gonorrhoeal discharge does not heal nicely, and as the parts are tender the patient objects to the manipulation necessary in using injections or irrigations. A narrow meatus prevents the free escape of the discharge and may even interfere with injections ; it is questionable, however, whether the meatus should be slit up.

Irritable sphincter.—In some men the urethra and sphincter are so sensitive that any attempt to irrigate produces a spasmodic contraction. This irritability generally passes off in

a few days, but in very early cases where it is important to begin the treatment as soon as possible, an injection of cocaine may be given to permit of the first one or two irrigations being carried out.

Penile oedema.—This occasionally follows the use of irrigations; it comes on suddenly soon after the treatment has been applied. If left alone it will subside in a day or two and treatment can then be resumed.

Haematuria.—This is sometimes seen after irrigations and is generally of mild degree. If it occurs it is wiser to suspend the irrigations till all traces of blood have disappeared from the urine. Occasionally it may be quite marked, and is then almost certainly due to cystitis or posterior urethritis.

Chordee.—In cases treated by irrigation this complication is rare. When the spasm is actually present the time-honoured practice of applying cold water affords considerable relief. In order to prevent a recurrence full doses of potassium bromide by day with an atropine and morphia suppository at bed-time should be tried.

Nocturnal Erections.—These are somewhat common when the posterior urethra is affected, and are a frequent cause of persistent acute inflammation, owing to the great hyperaemia of the parts annulling the effects of local treatment. Treatment must be directed to preventing the occurrence of erections by giving full doses of sedatives, especially potassium bromide, and by employing atropine suppositories.

Complications due to Extension along the Natural Passages.—*Epididymitis.*—This may occur at any time after the posterior urethra has become infected; frequently an epididymitis coming on without obvious cause is the first indication that the gonococcus is still present and active. The first sign is often an acute pain in the inguinal region. The vas deferens is at first much swollen, knotty and hard.

Treatment.—Injections of gonococcal vaccine will in most

cases exert a marked beneficial effect and should always be given irrespective of the local treatment. The man should be put to bed and the testicle supported so as not to allow any dragging on the cord. This can be accomplished by placing a folded newspaper across his thighs, which supports the testis as long as the man lies on his back, but fails if he turns over. For this reason it is better to employ some form of suspensory bandage: the one described below is the simplest and most efficient. When the pain is very acute rapid relief may be procured by puncturing the tunica vaginalis freely. The local application of warmth gives great relief in the early stages; a little later belladonna and glycerine is useful, while, when the subacute condition is reached, some form of counter-irritant is indicated. Ten to 20 per cent. of guaiacol in vaseline does well; strong medicaments, such as tincture of iodine, are not usually necessary, and they are liable to cause severe inflammation of the scrotum. Irrigation or injections need not be suspended unless the testis is so painful as to prevent the man leaving his bed without great discomfort.

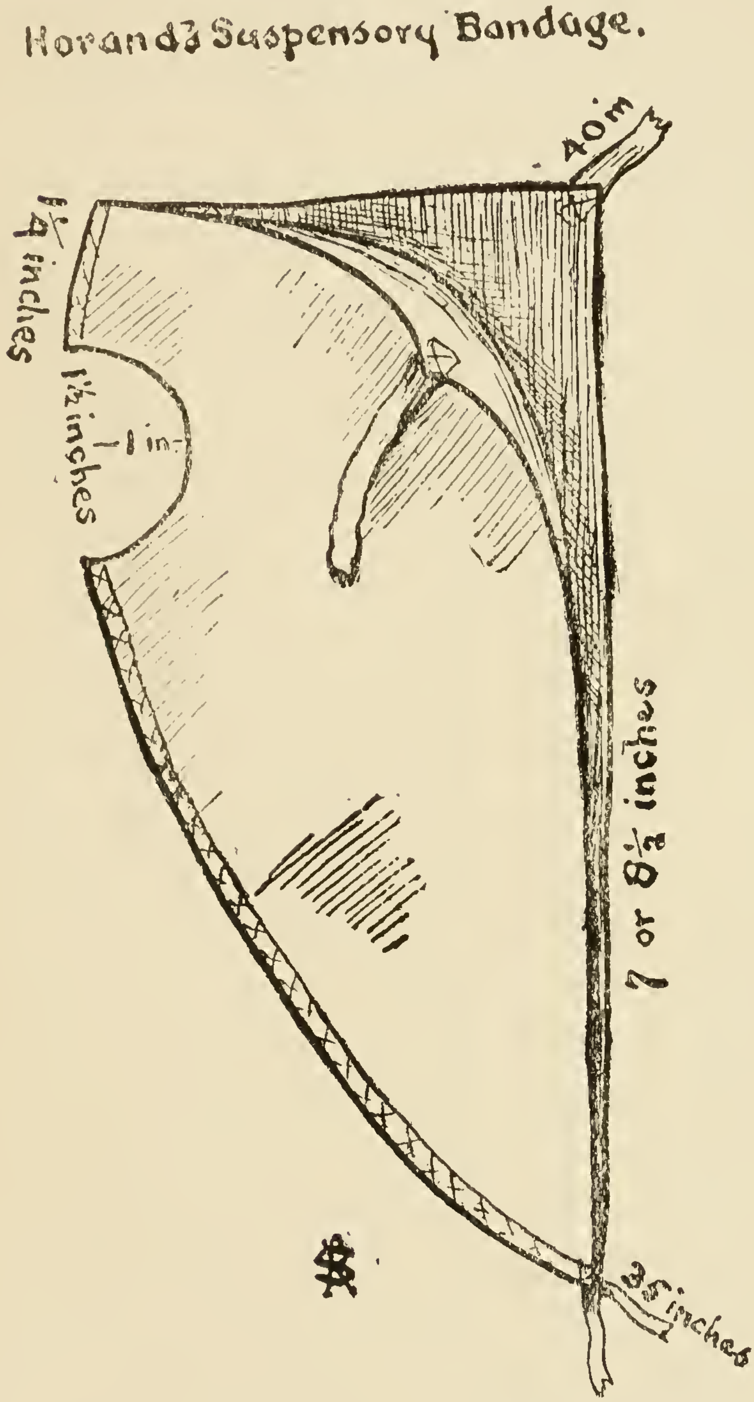
Abscesses.—These probably arise owing to the duct of an infected gland becoming blocked and so preventing the escape of the inflammatory products.

They may occur in the penis, one of Littré's glands being the starting-point; or in the perineum, due to infection of Cowper's glands; or the prostate itself may be the seat of suppuration. Wherever situated they are to be opened as soon as pus is detected and drained in the usual way; it is of interest to examine the pus for gonococci, as these are commonly found. A urethral fistula does not usually remain.

Bubo.—These occur occasionally in connexion with gonorrhoea, and are to be treated in the usual way; gonococci are not often found in the pus, at least by microscopical examination. Many of the so-called non-venereal bubos are prob-

N.B.—This diagram shows the bandage folded.

This is cut out of calico, and is usually made in two sizes, the measurements of which are noted on the diagram. The double line on the curved margin shows where the two halves are joined to complete the bandage. A broad tape is sewn to each of the upper points and two finer ones to the lower point.



Lower point.

Fig. 16.

To apply the bandage.—Place the lower point under the scrotum, carry the finer tapes backwards, round the thighs, and tie off in front of the abdomen. Next raise the swollen testicle as high as it will go, and support it with one hand, using the other to place as much cotton wool under the testicle as is necessary to keep it in this position. Bring the bandage over the whole, passing the penis through the aperture left for it; pass the broad tapes round the waist and tie off in front. The smaller tapes should then be interlaced with the broad ones and retied, as they have a tendency to slip down. A little more wadding may be required at the sides to adjust the pressure evenly.

ably due to old encysted gonococci; at least the frequency of a history of gonorrhoea is somewhat striking.

Cystitis.—This occurs to a greater or less extent whenever the posterior urethra is affected, but does not demand any special treatment. Very rarely the gonococcus invades the ureters and even reaches the pelvis of the kidney, giving rise to a pyelitis with considerable constitutional disturbance. Should this happen the man is to be kept at rest in bed, placed on milk diet with barley water, etc., and injections of gonococcal vaccine should be given.

Venereal Warts.—These have been ascribed to the irritation caused by gonorrhoeal discharges and some authorities even go so far as to say that the presence of venereal warts is diagnostic of gonorrhoea; this is much too sweeping a statement to make. The little growths are most commonly found in conjunction with phimosis, and it is difficult, if not impossible, to cure them permanently unless the foreskin be removed. This is one of the first steps which should be taken. As regards the local treatment of the growth, if they are pedunculated, as is frequently the case, the pedicle may be snipped through and the base touched with an escharotic, liquefied carbolic acid being the most generally useful drug. If the warts consist of masses of sessile-strawberry-like growths the attempt to remove them surgically is always unsatisfactory. Portions may be removed under cocaine and adrenalin anaesthesia, a ligature being temporarily applied to the penis, as the growths are very vascular and the bleeding obscures the parts to be operated on. If the patient is not pressed for time he can attend twice or three times a week as an out-patient and have some medicament applied. Nitric acid is very painful, glacial acetic acid is not pleasant, carbolic acid is not painful but does not penetrate sufficiently and takes a long time to effect the destruction of any large mass. Copper sulphate, caustic potash, washing soda in

crystals and a large variety of substances have been recommended at different times. The most satisfactory application is equal parts of liquor epispasticus and tincture of iron. Whenever any irritating preparation is used on or near the glans penis it is always advisable to cover the surrounding surface with a layer of vaseline or other greasy substance, as this prevents any extension of the irritation.

In one case a large cauliflower warty growth disappeared after several exposures to X-rays.

Spread of Infection by means of the Blood Stream.—Synovial and endothelial membranes are specially susceptible to the gonococcus, although almost any tissue may be attacked. The commonest metastatic lesion is arthritis; other lesions are iritis, conjunctivitis, endocarditis, hyperkeratosis of the skin, periostitis, arteritis, phlebitis and peritonitis. The most efficient remedy, provided it is given early in the onset of the lesion, is gonococcal vaccine, and this should always be employed in full doses as soon as the condition is recognized. Treatment of the particular lesion, on the usual lines, should at the same time be carried out; this is specially necessary in the case of arthritis.

Gonorrhoeal ophthalmia.—This condition requires immediate treatment, hence if suspected the pus should be examined microscopically for gonococci and in the meantime treatment should be begun. Nitrate of silver is the most efficient drug, but on account of the extreme irritation it causes must be used in very dilute solution, such as half a grain to the ounce of distilled water. The solution requires to be used frequently, say, every half hour by day and at least two hourly by night. Better results are obtained by using one of the newer silver salts, such as protargol 1 grain to the ounce or albargin $\frac{1}{4}$ grain to the ounce, every half hour by day and every two hours by night. Much of the success depends on the thoroughness with which the washing out is

done: the solution must be made to penetrate into every corner of the conjunctival sac, and the margins of the eyelids require special attention. If the disease has become fully developed when the case is first seen heroic measures are excusable in order to save the eye: cocaine may be applied to make the surface insensible, and then a 1 per cent. solution of silver nitrate, or 2 per cent. protargol, or a ½ per cent. albargin solution used for the first two or three applications, after which the weaker solutions should be employed. As usually only one eye is affected at first, the other must be protected by a watch-glass shield to prevent it from becoming infected.

TEST OF CURE

How is one to know when a man is cured of gonorrhoea? This is always a very difficult question to answer, in fact it used to be said in Germany that every attack is curable with the exception of the first; this is of course an exaggeration, but it emphasizes the difficulty of the question. No infallible test has yet been devised. The ancient test of squeezing the pipe to produce a drop of discharge is absolutely useless, as can be easily shown by applying the "two glass test" to a number of men who fail to produce any secretion after vigorously squeezing the penis.

The following plan will suffice in most cases, although it is by no means free from error. When the urine has been clear and free from threads for two days, stop all treatment for another two days. If still satisfactory put the man on full diet with beer and if possible also pickles, and employ him on all fatigues. If the urine is still free from evidence of disease at the end of at least four days of this regimen, the man may be discharged as cured. If threads persist one of these should be fished out and examined microscopically for gonococci; failure to find these does not prove their absence, and

if many pus cells are present a strong suspicion may be entertained that some are still lurking in the recesses of the urethra or its accessory glands. An injection of a 1 per cent. solution of nitrate of silver may then be tried ; this will produce a free discharge, in which the gonococci may be detected. A better test of cure, although not an infallible one, may be carried out as follows : The urethra is washed out with physiological salt solution, some of which is injected into the bladder. The prostate is then massaged and the expressed secretion examined microscopically for gonococci. The salt solution in the bladder is then passed into a test glass and centrifugalized. The sediment is stained and examined for gonococci.

Recapitulation of the Main Points in Treatment.—Gonorrhoea is caused by the gonococcus, remove this and the disease ceases. The gonococcus at first is on the surface and open to attack.

Don't wait till it has established itself in the sub-epithelial layer and has to a great extent become protected from the action of any medicament introduced into the urethra.

The secret of obtaining rapid cures is early treatment, therefore impress on every man that, if he has exposed himself to infection, he is to report sick, if he has any *suspicion* of having contracted gonorrhoea. From the fourth to the eighth day after infection, each day passed without treatment means one to three *weeks* longer in hospital. See each man's urine daily (not another man's, as the soldier will show this if he thinks he can get out of hospital by means of this trick) and vary your treatment according to the state of the urine.

Weak solutions used frequently are preferable to strong ones at longer intervals. Do not order treatment too strong or too long ; if the results are disappointing, try a few days' complete rest. Before discharging a man as cured, apply some test to make sure that the disease has been eradicated.

If a true relapse takes place, the gonococcus has been lying

latent in one of the accessory glands, most probably the prostate.

Fitness for Active Service.—When examining soldiers as to fitness to proceed on active service, the medical history sheet is of course seen. If this shows repeated entries for gonorrhoea, it is as well to inquire as to any indications of stricture and even to pass a bougie. If, however, there is only one, or at most two entries, and the man has been doing full duty for at least three months, no further notice need be taken. In the case of a recent admission for gonorrhoea, in which the man has been less than three months out of hospital, it would be advisable to see a specimen of his urine and make certain that the disease has been cured.

GONORRHOEA IN WOMEN AND CHILDREN

Medical officers in charge of families and cantonment hospitals in India may have under their care women and children suffering from gonorrhoea; it has therefore been considered advisable to include a short account of the disease in women and children.

In the Adult Female.—*Sites of Infection.*—The cervix uteri, the urethra, or both are the parts first infected; the vagina on account of its surface being covered with squamous epithelium usually escapes or does not become infected till a later date and then only to a mild extent. From the cervix uteri the infection may extend upwards into the body of the uterus and produce an endometritis; from there it may spread along the Fallopian tubes, setting up a pyosalpingitis or reach the peritoneum and set up a local peritonitis, i.e. a perimetritis. The infective discharge from the cervix trickling into the vagina infects the urethra, if this has not already happened, and in many cases the ducts of Bartholin's glands. Pus escaping from the vagina causes a gonococcal infection of the rectum in roughly half the number of cases.

In acute cases the vagina is inflamed and painful, sometimes extremely so, and there is a copious purulent discharge in which gonococci are plentiful. Micturition may be painful, but never to the same extent as in the male. In subacute cases the discharge varies in amount, but is usually scanty and thinly purulent; gonococci are present, but in relatively small numbers. Pus can be squeezed from the urethra, and the cervix when examined by means of a speculum generally shows some erosion and a purulent discharge.

In chronic cases the symptoms are usually ill-defined. There may be a varying amount of discharge at intervals; inflammation is very slight or absent and the urethra and cervix only contain a thin muco-purulent secretion.

Diagnosis.—This really depends on finding gonococci in the discharge which in subacute and chronic cases may not be an easy matter, as the gonococci are obscured by the numerous other germs present in the secretion.

Prognosis.—As regards cure the prognosis is by no means good. When the gonococci have established themselves in the glands of the mucous membrane lining the cervix uteri, it is impossible to attack them successfully by any external application; they may persist in this situation for years without giving rise to any very definite symptoms, while still retaining their power to infect healthy mucous membrane. If infection of the pelvic organs takes place the prognosis is serious owing to the adhesions produced in the organs of generation. Thus barrenness may ensue, or if conception takes pace the foetus may be expelled at an early period, or again a tubal pregnancy may result. Should a pyosalpinx form, a laparotomy will probably be required.

Treatment.—During the acute stage the patient should be kept in bed and given a light diet. We do not think that any drug in the form of a mixture can exert a direct effect on the

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course of the disease ; sedatives may be employed to relieve pain. Injections of gonococcal vaccine should be given and if well tolerated should be freely pushed in the hope of raising the patient's resistance and so checking the spread of the disease. When the cervix is infected suppositories of atropine should be employed in order to preserve the Fallopian tubes from infection.

Copious vaginal douches, as hot as the patient can bear, should be employed thrice daily. Permanganate of potassium, 2 grains to the pint, is a useful solution, but the actual medicament employed is of minor importance provided the solution is weak, the object being merely to wash away the gonococci and toxin and to produce a mild hyperaemia of the parts. If the labia are swollen and painful a piece of lint coated with some soothing ointment should be placed between them. An absorbent pad of some mildly antiseptic substance should be kept constantly over the vulva to prevent the discharge from reaching the rectum.

In subacute and chronic cases gonococcal vaccine should also be tried and the vagina should be douched. The cervix uteri and the urethra should be swabbed with ½ to 1 per cent. solution of nitrate of silver or a corresponding strength of one of the organic silver salts. Schindler's jelly should prove most useful in these cases.

If an abscess forms in one of the ducts of Bartholin's glands it should be opened and drained ; in some obstinate cases it may be necessary to dissect out the affected portion of the duct.

Vulvo-vaginitis of Infants.—Gonococcal vulvo-vaginitis is extremely contagious in little girls under five years of age, and if introduced into a children's ward may spread in epidemic form. The infection may be derived from the mother's fingers or from an infected sponge or other article of toilet ; as long as the gonococcus remains moist it retains its virulence,

hence the strictest isolation of the patient must be maintained. Any child admitted with a vaginal discharge must be kept under careful observation and the discharge must be repeatedly examined for gonococci.

Diagnosis.—This can only be definitely formed by finding gonococci in the discharge.

Prognosis.—This is much the same as in the adult female, that is to say, it is extremely difficult to eradicate the disease, while any of the complications of gonorrhoea in the adult female may equally occur in the child. If the pelvic organs are attacked the intensity of the process is much less than obtains in the adult female, but permanent barrenness may result from the formation of adhesions.

Treatment.—This is very unsatisfactory. Owing to the minute size of the parts local applications cannot be thoroughly employed. Injections of small doses of gonococcal vaccine should always be given a trial. Frequent hot douches with some non-irritating solution should be prescribed ; prolonged hot hip baths should prove useful ; cleanliness of the affected parts should be ensured.

CHAPTER XV

SOFT CHANCRE

Soft chancre is a contagious ulcer of the genitals which is generally attributed to inoculation with the bacillus of Ducrey. In contrast to the hard sore it is autoinoculable. It may become phagedenic or diphtheritic and almost always gives rise to a suppurating bubo which may exceptionally prove very intractable, spreading over the abdomen or across the thigh in a serpiginous manner and defying every surgical measure.

Aetiology.—It is possible that the term soft chancre is applied to a number of ulcerative lesions of the genitals which are due to more than one organism. The most constant micro-organism which has been found in soft chancre and the ulcerating buboes to which it gives rise is the bacillus of Ducrey, a short thick rod which is Gram-negative and arranged as a strepto-bacillus in short or long chains which are very characteristic. The aetiological relationship of Ducrey's bacillus to soft chancre rests on the constancy of its presence and the result of inoculations on man, but the evidence from the effect of vaccines prepared from this bacillus appears so far to have been negative. Herbst and Gatewood tried a vaccine prepared from a doubtful Ducrey's bacillus on several cases of soft chancre but with poor results. They then used a vaccine prepared from a diphtheroid bacillus isolated from one of their cases, with beneficial results.

Independently of these workers, Lieut. Harold, R.A.M.C., isolated from a phagedenic sore, which had defied all surgical treatment for seven months, a diphtheroid bacillus and treated the patient with a vaccine prepared from it. The result was an intense local reaction at the site of the sore, and, under successive doses of vaccine, the sore healed in five weeks. Subsequently, he treated with this vaccine three cases of ulcerating bubo from which he isolated the same diphtheroid bacillus, with beneficial results in all of them. It seems clear from the observations of these workers that Ducrey's bacillus is not invariably the cause of soft chancre, as is so frequently taught.

Diagnosis.—From the point of view of treatment, the first point to settle is whether a sore is syphilitic or not, since many sores which have the appearance of a soft chancre contain the micro-organism of syphilis. The surgeon should not be content with a negative microscopical examination, but should make three examinations of the blood at monthly intervals, since if syphilis is not demonstrable at the first examination it may be incubating in the sore. Subsequently, the intractability of the sore or resulting bubo to ordinary measures may demand a bacteriological examination.

For Ducrey's bacillus Queyrat recommends the following stain :—

Ziehl's fuchsin, 10 drops ; saturated solution of methylene blue, 7 drops ; distilled water, 20 c.c. Stain for ten minutes.

The protoplasm is coloured red, the bacilli and nuclei violet.

The diptheroid bacillus isolated by Harold is a short Gram-positive rod which shows marked bi-polar staining, especially with carbol-thionin. In film preparations it is frequently seen lying in parallel rows like a short pallisade. It does not form chains, and in cultures a few days old involution forms are frequent ; the most common of these are swollen and elongated

or club-shaped, the enlarged ends being occupied by polar granules.

Treatment.—There are two main lines of treatment; the first is to attempt to destroy the bacilli and so convert the specific sore into a simple ulcer, the other is to maintain surgical cleanliness and trust to the natural powers of recovery.

Under the first plan may be included the complete excision of the sore with suturing of the wound; this plan, although theoretically excellent, has been very disappointing in practice, as the wound almost always becomes infected by the specific bacilli, hence the result is merely to produce a much larger sore.

The bacilli may be destroyed by keeping the surface of the chancre at a high temperature, or an attempt may be made to destroy the bacilli along with the diseased tissues, by means of the actual cautery or of chemical escharotics; the latter methods, however, are likely to cause considerable inflammation of the parts and hence should be reserved for small sores of recent origin. The most satisfactory method of obtaining a constant high temperature is that employed by Welander of Stockholm; he applies a moist dressing to the surface of the penis, outside this, Leiter's coils are wound, and, by means of a special apparatus, water kept at a temperature of 130° F. is made to circulate; the sore is thus kept at a temperature of 106°F. After 24 hours of this treatment, all the bacilli are killed, and the chancre has become a simple ulcer; if possible, the application of heat should be continued for three days, as the high temperature greatly facilitates healing, which, under this treatment, should be complete in eight days. The great objection to this plan is that a special heat regulator is required for each case under treatment.

Heat can also be applied by means of Hollaender's hot air apparatus. In its present form this is a somewhat severe procedure and is in fact merely another form of cautery; it

might possibly be modified so as to become a really useful form of treatment. The actual cautery may be applied to the chancre or a glowing cautery may be held as close as possible to the sore, without actually touching it, for fifty seconds. Bathing, with very hot water for an hour at a time, is stated to hasten the process of healing.

The two substances most often used for the purpose of destroying the bacilli are nitric acid and pure carbolic acid. The former is very painful and causes a great deal of oedema. Carbolic acid is much less irritating and probably more efficacious; it should be applied lightly to begin with, and then well rubbed in. Silver nitrate is not to be recommended as a germicide in chancres, as it fails to penetrate the tissues sufficiently, and it gives rise to great irritation.

On the whole the destructive plan of treatment does not yield very satisfactory results, and it always leaves more or less induration which may, if seen by a surgeon who is not acquainted with the treatment which has been followed, give rise to the idea that the sore was originally a hard one.

In most cases better results will be obtained by the employment of milder measures than those given above.

The point is thoroughly to cleanse the surface of the sore, and get rid of all pyogenic germs which are usually abundant there. Peroxide of hydrogen sprayed on will get rid of the yellowish covering so often met with; if this remedy is not available, frequently changed dressings of moist boric lint are useful. When the surface has become clean and fresh, the chancre should be treated much like an ordinary indolent ulcer. The following general rules may be of service to those who have not had an extended experience.

When there is much discharge, use wet dressings in preference to dry powders, as these are likely to mix with the discharge, forming scabs which retain the pus and prevent healing. Ointments, as a general rule, are less effective than non-

greasy preparations. The application should be varied from time to time according to the state of the sore, thus a stimulating preparation for a few days followed by a soothing one accelerates the process of repair. Mercurial preparations must not be used if there is any suspicion of syphilis, as the course of the disease may be so modified as to obscure the diagnosis.

A great variety of preparations have been recommended at different times, but after a little experience each surgeon will naturally select his favourite formulae. A certain number are given in Appendix VIII as a suggestion for those who have not had much experience in the treatment of soft chancres.

Chancre with Phimosis.—When a chancre occurs under a long foreskin, there is often a great deal of inflammation, and the prepuce cannot be retracted. If left alone phagedena may ensue; the most rapid way of exposing the sore is to slit up the prepuce; this should not be done until a trial has been given to the following plan. Syringe out the foreskin with any mild antiseptic and then inject carbolic oil or an oily emulsion of iodoform. The oil seems to act mechanically, keeping the surfaces apart and allowing the discharge to escape freely.

Phagedenic Chancre.—The best treatment is, of course, the continuous hot bath with some mild antiseptic in the water. Very good results can, however, be obtained by dusting the sore thickly with one part of iodoform and three of charcoal, and applying a boric fomentation over this; the dressing should be changed every four hours, after spraying with peroxide of hydrogen. Strong antiseptics, such as nitric or pure carbolic acid, must be used with care, as they are apt to destroy the remaining vitality, and so lead to an extension of the gangrenous process. An autogenous vaccine should if possible be employed (see Aetiology, p. 276).

Fitness for Active Service.—As long as a soft chancre is

present, it is not advisable to permit a man to proceed on active service, as at any time a bubo may form and incapacitate him for some considerable time. If his medical history sheet shows a recent entry for soft chancre, special attention should be paid to the inguinal lymph glands when examining the man for active service.

Bubo.—Bubo, or acute inflammation of the inguinal lymphatic glands, may occur in connexion with soft chancre, gonorrhoea, or as the result of strain tearing the efferent lymph vessels, or in consequence of the absorption of septic matter through an abrasion in the skin. In all probability the lesion following soft chancre is also due to the absorption of pyogenic germs at the site of the sore. Most bubos break down and form an abscess; occasionally an ulcerating surface is left and the destructive process tends to spread to neighbouring parts. The gonococcus appears to have the property of remaining encysted for long periods without causing any trouble, but on the occurrence of some slight mechanical injury it becomes active and soon leads to the formation of an abscess.

Treatment.—The first and most important point is to place the patient in bed and insist on absolute rest. The next is to apply pressure in the hope of promoting absorption. As to local applications, sometimes hot fomentations, at others counter-irritants, or again soothing remedies, such as belladonna and glycerine, may be found to give best results according to the case.

If suppuration takes place freely, the abscess is to be incised and treated on the usual surgical lines. When, however, suppuration is limited to a few minute centres, it is better to give an anaesthetic and thoroughly scrape the swelling, removing all diseased tissue. The wholesale excision of lymphatic glands is hardly to be recommended, as the healthy tissue is taken away along with the diseased, and lymph-

oedema may ensue. The sharp spoon does not remove the healthy portions of the gland.

In some cases the gland assumes a chronic indurated condition, which will neither resolve nor suppurate. In such cases the following plan will often promote absorption. The swelling is to be painted each morning with tincture of iodine. The negative electrode of a galvanic battery is then to be applied for ten minutes, using about 5 milliampères, or stronger if the man can bear it. If no improvement results in a week, an attempt to induce suppuration by injecting 5 minims of pure carbolic acid should be made. If, as usually happens, this is successful, the gland can be dealt with by incision and scraping.

BALANITIS

is a peculiar inflammatory condition with superficial circinate erosions of the glans penis. It is usually associated with a profuse secretion of offensive pus. When the same condition affects also the mucous membrane of the prepuce it is known as Balano-posthitis.

Aetiology.—Though it may complicate Gonorrhœa, Chancre, or Chancroid, it does not depend on any of these, since it may occur independently. No particular micro-organism has been incriminated as the causal agent; the secretion swarms with micro-organisms of all kinds, but, as far as we know at present, all of these are to be found in the normal secretions of this region. In its more severe forms it is most frequently associated with a long prepuce, especially with phimosis, which may be either natural or the result of inflammatory swelling. Such a condition lends itself to retention of natural secretions, and quite possibly it is the fermentation of these which irritates and superficially erodes the surface.

Symptoms.—There is generally some irritation, with scalding on micturition. The prepuce is frequently swollen,

sometimes very greatly, and pus with a peculiarly offensive odour oozes freely, or is easily expressed, from the mouth of the prepuce. If the prepuce can be retracted, the glans penis, the sulcus behind it and the mucous membrane of the prepuce are often found to be eroded. The erosions are very superficial, leaving smooth red circinate patches which are quite characteristic.

Microscopical examination of the pus shows, besides multitudes of pus cells and some epithelium, swarms of microorganisms, especially spirochetes. These vary in size from coarse *Sp. refringens* to spirochetes which are so fine and have such closely-set spirals that the inexperienced observer may easily mistake them for *Sp. pallida.*

Diagnosis.—Patients with balanitis are frequently sent to hospital diagnosed gonorrhœa, and it is only when the prepuce is retracted that the absence of any discharge from the urethra is discovered. The circinate erosions are easily distinguished from those due to syphilis, but in case of doubt a specimen of the serum from beneath the thoroughly cleaned sore should always be examined microscopically.

Gonorrhœa or syphilis may, of course, coexist, and it is very important to make a thorough examination of every case of balanitis to determine the presence or otherwise of these more important diseases. On account of the phimosis such an examination may be particularly difficult. It is certainly unpleasant.

Treatment.—The secretion should be removed by syringing behind the prepuce with some mild antiseptic and astringent solution, e.g. boric acid lotion followed by a weak lead lotion several times a day. It may be necessary to expose the affected area by circumcision, and, though circumcision wounds do not heal well under such conditions, if there is any suspicion that a chancre is present behind the tight prepuce it is much the best plan to lay open the prepuce in order to reach the sore and make an early diagnosis.

Appendix I

TABLE I. UNITED

AVERAGE NUMBER CONSTANTLY SICK AND
PER 1,000 OF

	1880	1881	1882	1883	1884	1885	1886	1887	1888	1889	1890	1891	1892
— SYPHILIS.													
Constantly sick	9·53	10·17	10·28	11·61	13·15	12·31	10·34	10·31	10·13	9·09	9·95	8·82	9·46
Invalided	·71	·44	·61	·63	·56	·53	·48	·64	·93	1·05	·81	·72	·70
GONORRHOEA.													
Constantly sick	6·71	6·50	6·93	6·93	6·99	7·03	7·05	6·34	6·06	6·25	5·97	5·55	6·10
Invalided	—	·05	·10	·01	·07	·05	·02	·05	·03	·07	·03	·04	·07

TABLE II.

AVERAGE NUMBER CONSTANTLY SICK AND
PER 1,000 OF

	1880	1881	1882	1883	1884	1885	1886	1887	1888	1889	1890	1891	1892
SYPHILIS.													
Constantly sick	—	8·08	8·81	8·84	8·46	10·77	11·41	8·76	8·39	15·91	18·13	15·35	14·49
Invalided	—	·49	·42	·46	·18	·35	·18	·35	1·11	·95	1·05	1·69	1·09
GONORRHOEA.													
Constantly sick	—	6·67	8·22	8·46	9·89	10·64	10·17	10·02	12·36	13·11	12·55	10·92	11·45
Invalided	—	—	·01	—	·01	·01	·01	—	1·	·01	·01	·01	·03

KINGDOM.

INVALIDED FOR SYPHILIS AND GONORRHOEA
STRENGTH.

1893	1894	1895	1896	1897	1898	1899	1900	1901	1902	1903	1904	1905	1906	1907	1908	1909	1910
9·10	8·79	8·09	7·79	6·66	6·28	5·18	3·09	4·18	4·67	4·49	4·09	3·14	2·78	2·59	2·17	2·18	2·20
·74	·83	1·05	1·30	1·04	1·29	1·06	·83	·90	1·27	·88	·92	·66	·42	·25	·3	·23	·28
6·25	5·81	5·41	5·03	4·82	4·55	4·01	3·23	4·22	4·21	5·13	4·35	3·95	3·42	3·36	3·33	3·11	3·40
·04	·12	·02	·10	·16	·11	·07	·05	·09	·10	·09	1·69	1·49	·06	·17	·13	·14	·21

INDIA.

INVALIDED FOR SYPHILIS AND GONORRHOEA
STRENGTH.

1893	1894	1895	1896	1897	1898	1899	1900	1901	1902	1903	1904	1905	1906	1907	1908	1909	1910
17·65	22·54	25·16	24·97	23·76	17·29	13·17	10·93	9·42	8·33	8·36	5·45	4·80	3·55	3·02	2·37	2·23	2·01
·34	1·41	1·74	1·90	5·57	4·44	2·28	·97	·75	1·42	1·02	·68	·80	2·17	1·48	1·34	·58	·48
13·55	14·24	15·67	14·70	15·65	10·68	9·38	10·26	8·93	9·27	8·31	7·60	6·52	5·80	5·63	4·80	4·98	4·60
·04	·15	·16	·12	·35	·26	·15	·08	·03	·07	·09	·13	·08	·2	·34	·35	·17	·2

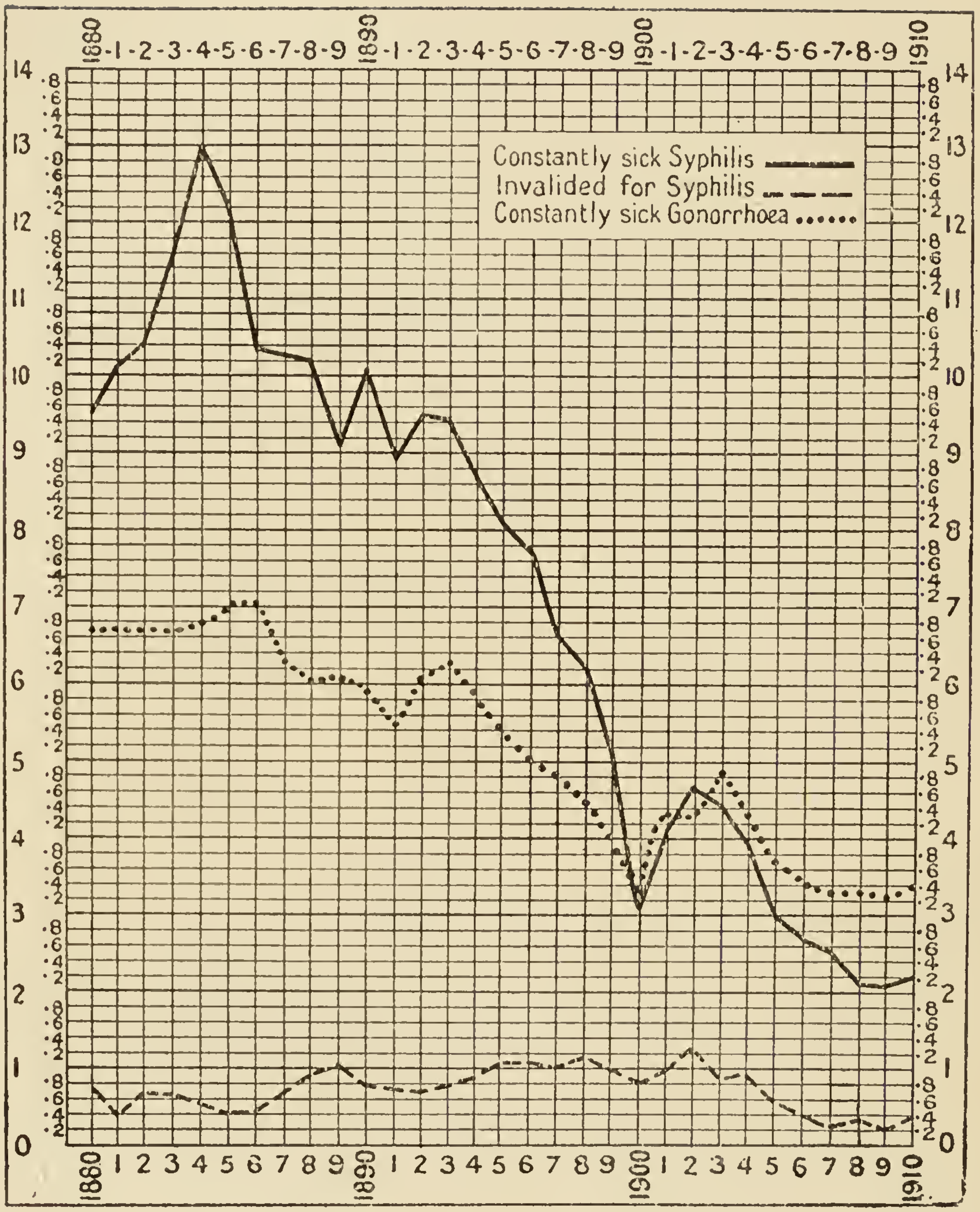

CHART I. (*See page* 3.)

FOR TROOPS IN THE UNITED KINGDOM.

From 1880–1910 inclusive.

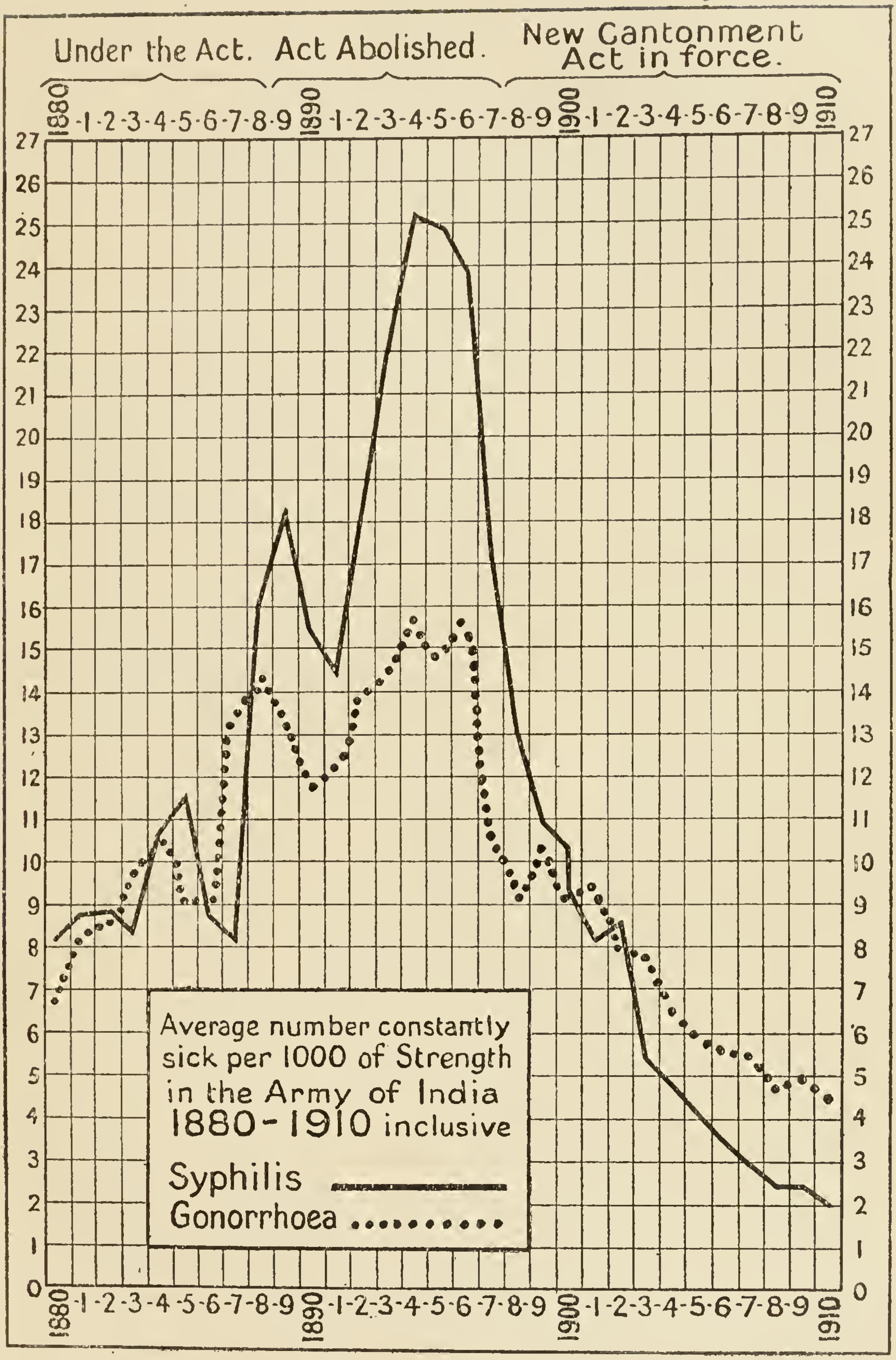

CHART II. (*See page* 5.)

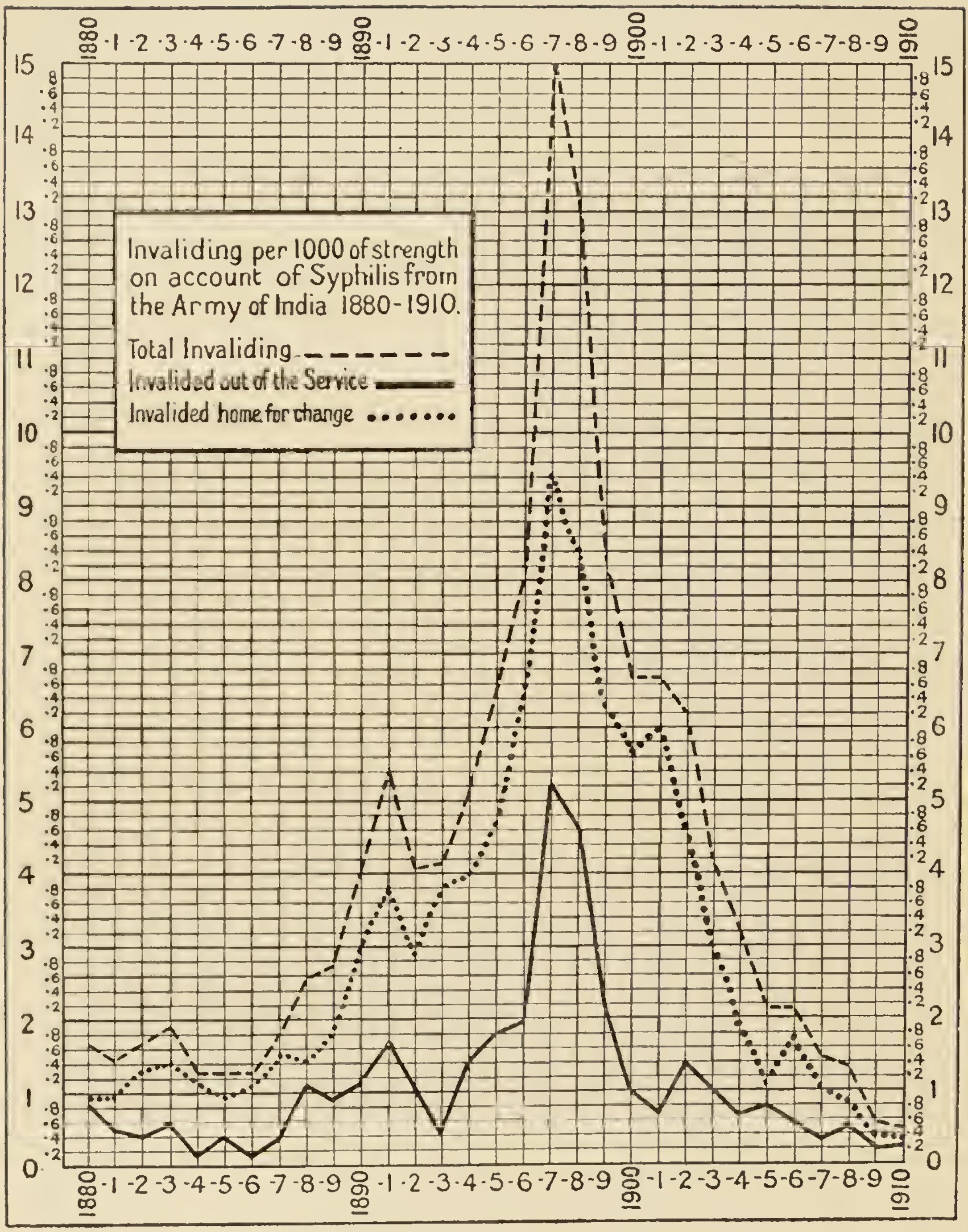

CHART III. (*See page* 7.)

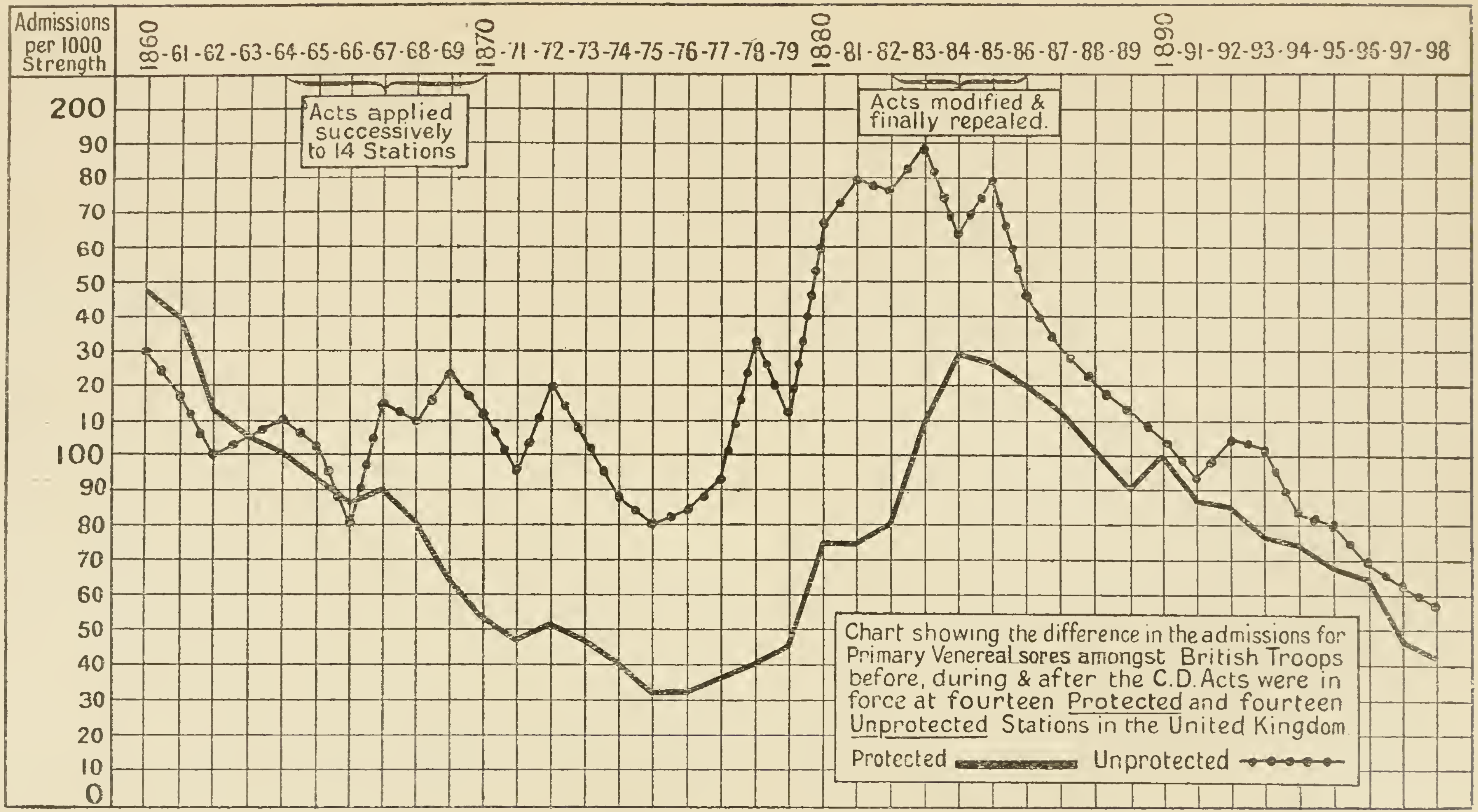

CHART IV. (*See page* 10.)

(Prepared by Col. W. G. MACPHERSON, C.M.G.)

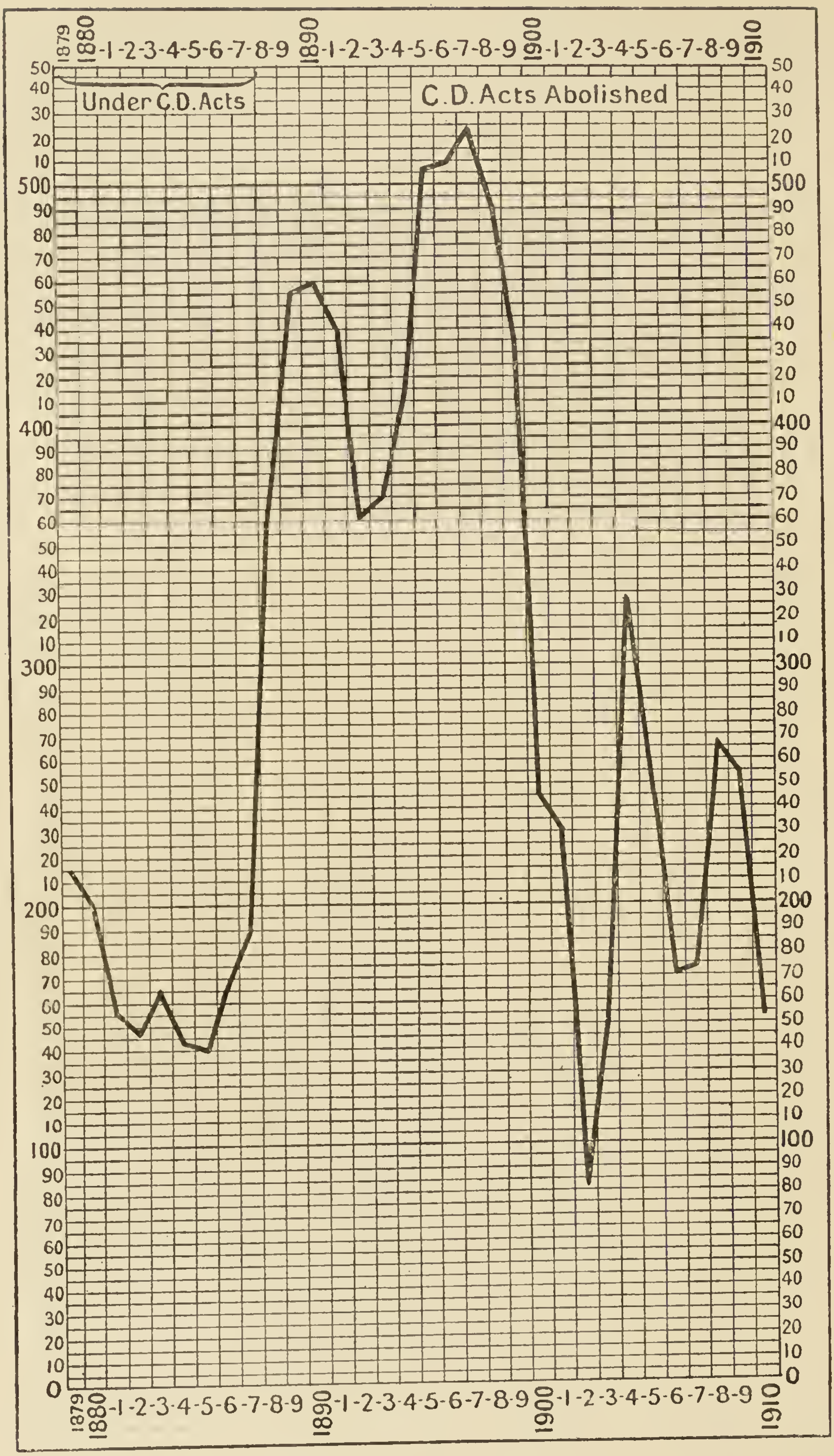

CHART V. (*See page* 13.)
Admissions per 1,000 for all Venereal Diseases, China and Straits Settlements, 1879–1910.

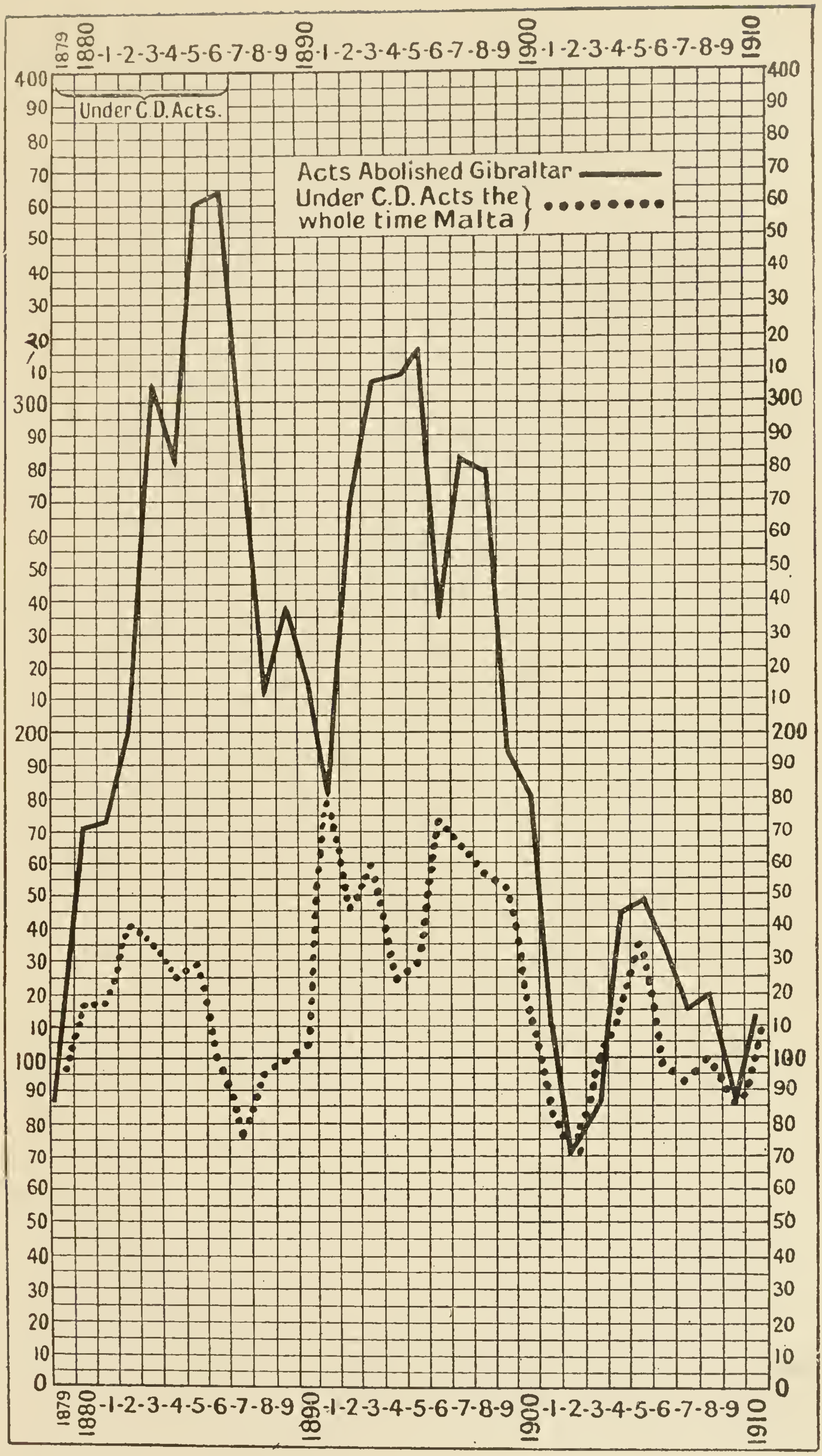

CHART VI. (*See page* 13.)

Admissions per 1,000 for all Venereal Diseases, Gibraltar and Malta, 1879–1910.

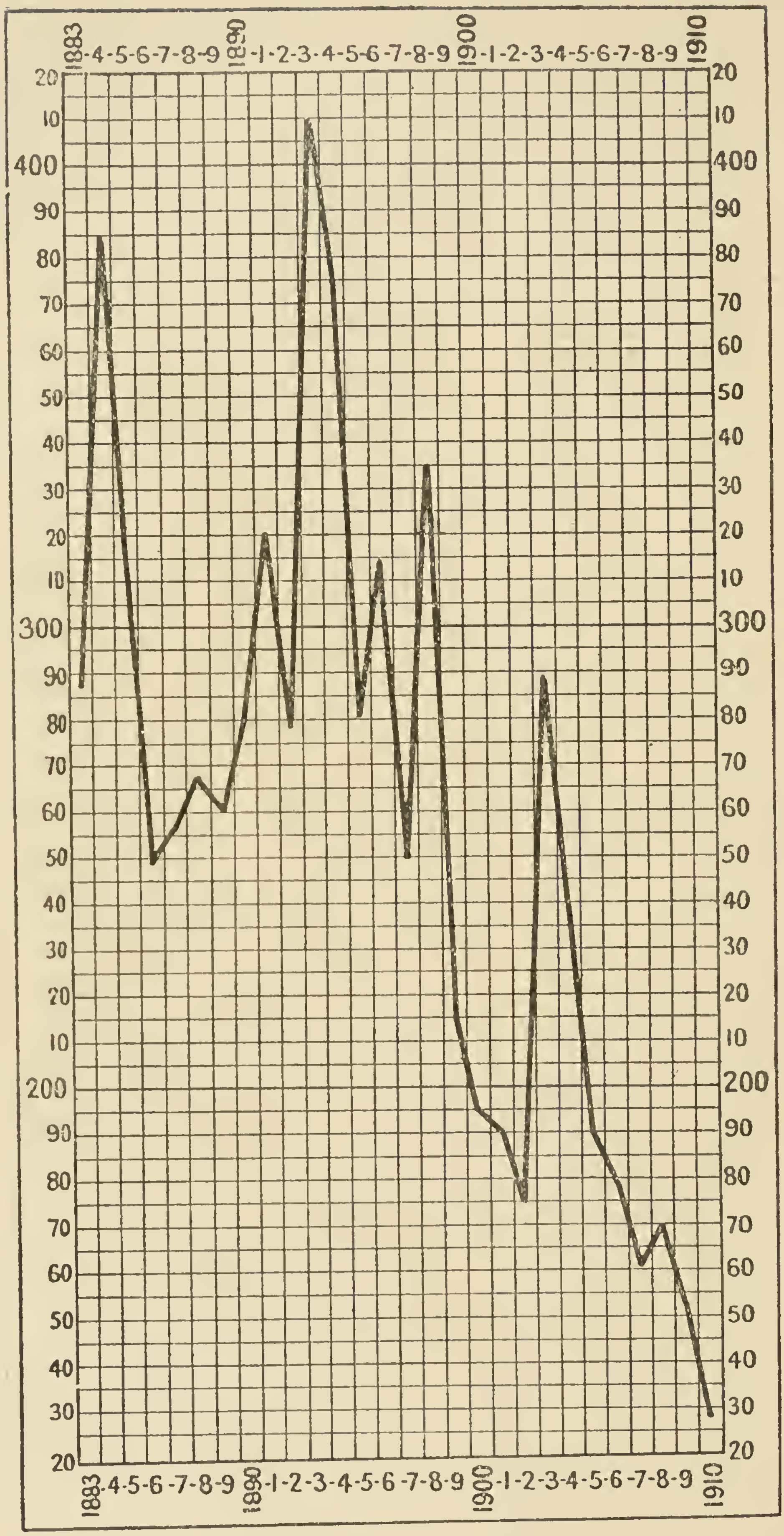

CHART VII. (*See page* 13.)

Admissions per 1,000 for all Venereal Diseases, Egypt, 1883–1910.

Appendix II

(*See page* 87)

EXTRACTS NOT GIVEN IN DETAIL IN THE TEXT

(1) Noguchi

Extract liver (syphilitic or normal) or kidney (beef kidney can be used) with ten volumes of 95 per cent. alcohol for six or seven days at 37°C. Filter through filter paper and evaporate to dryness at a temperature below 40°C. Extract the resinous residue with ether and allow the ether extract to evaporate to dryness. Dissolve the residue with a small quantity of ether and add five volumes of acetone. Allow the precipitate to settle and decant the supernatant fluid carefully. Allow the remainder of the acetone to evaporate and keep the resinous residue in an air-tight jar.

For the test dissolve a little of the resinous mass in a small quantity of ether and make a 0·2 per cent. suspension of the ethereal solution in 0·85 per cent. saline.

If kept on ice the emulsion is fairly stable.

(2) Candler and Mann

Weighed syphilitic liver is ground up with silver sand and plaster of Paris and the powdered residue is washed with acetone to remove haemolytic and anticomplementary bodies. The acetone is poured away and the residue allowed to dry at room temperature and transferred to a flask. Sufficient alcohol is added to make 4 c.c. to every gramme of original liver and the mixture left at room temperature for two to three days before filtering.

It is stored in the refrigerator in dark bottles. (Quite probably normal solid organ could be used instead of syphilitic liver.)

(3) Browning, Cruickshank and Mackenzie's Lecithin-cholesterin [1]

The lecithin is extracted from ox liver in the following manner. A crude extract of ox liver is made by digesting it with four parts of 95 per cent. alcohol for three or four days at room temperature, the mixture being stirred at least once a day. After filtering, the extract is evaporated to a syrupy mass in a flat porcelain dish on a water-bath at 60°C.

The syrupy mass is rubbed up with quartz sand (about 50 grammes of sand to 1,000 c.c. of original extract). A firm mass results which is placed in a spherical flask closed with a rubber bung through which a piece of quill tubing drawn to a capillary point at the end.

Ethyl acetate is placed in the flask, which is then stoppered and immersed up to the neck in a water-bath at 60°C. The flask is shaken repeatedly and after ten minutes the ethyl acetate is filtered through fat-free paper in a hot-water funnel, the water in the funnel being kept at 60°C. More ethyl acetate is added to the residue in the flask and the process repeated. The residue is extracted with ethyl acetate a third time, a total of about 170 c.c. ethyl acetate being required to extract the residue of 1,000 c.c. crude extract.

The ethyl acetate solution is placed in the refrigerator over night and a precipitate falls out. The precipitate is taken and again dissolved in ethyl acetate at 60°C. and the solution put in the ice-chest another night.

The precipitate is dissolved in ether and the solution placed in a cylinder with four times its volume of acetone, which causes a precipitate. The mixture is shaken for some minutes to assist precipitation. After ten minutes the clear supernatant fluid is poured off and the precipitate dissolved again in ether. The precipitation with acetone is repeated twice.

The last precipitate is rubbed up with sand and extracted with pure ethyl alcohol (100 c.c. to the precipitate from 1,000 c.c. of original extract) at room temperature for twenty-four hours.

This makes the solution of lecithin. Its strength is estimated by taking from 5 to 10 c.c., evaporating at 57°C. to dryness and weighing the residue. It is made to a strength of 0·75 per cent.

[1] Sold by Messrs. Thomson, Skinner & Hamilton, 38 Sauchiehall Street, Glasgow.

Lecithin-cholesterin solution.—To the 0·75 per cent. solution of lecithin is added cholesterin (Kahlbaum or Poulenc Frères) in excess, 1 to 1·2 grm. to 100 c.c. of lecithin solution, and the mixture is shaken repeatedly. It is ready for use in about a week, but if required earlier solution of the cholesterin is assisted by brief and gentle warming on a water-bath.

This lecithin-cholesterin solution makes an excellent artificial extract for the ordinary original test. Its authors have elaborated a test based on the difference in the amount of complement which is deviated by a serum when in contact with the lecithin and the lecithin-cholesterin solution respectively.

Each solution is diluted to 1 in 8 by floating on saline, and of the emulsion 0·6 c.c. is added to 0·05 c.c. tested serum in each of a number of tubes. The respective mixtures are incubated with varying amounts of complement calculated in M.H.D. Browning and Mackenzie state that if a serum deviates two to three more doses of complement when in contact with lecithin-cholesterin than with lecithin alone, it is in favour of the serum being syphilitic, and if five or more doses are absorbed it is practically conclusive.

Appendix III

(*See page* 203)

MERCURIAL PILL FORMULAE AND PLAN OF TREATMENT

The commoner preparations given by the mouth are—

Pills—

Hydrarg. c. Creta, 1 to 2 grains, three to five times daily (or in powder).

Pil. Hydrarg. 1 to 2 grains, two to three times a day.

Salicylate of mercury, $\frac{1}{5}$ of a grain, three times daily.

Tannate of mercury, $\frac{1}{2}$ grain, three to five times a day.

Green iodide of mercury, $\frac{1}{6}$ to $\frac{1}{3}$ of a grain, three times a day.

Perchloride of mercury, $\frac{1}{7}$ of a grain, two or three times daily.

(The last two pills are favourite ones in France.)

Perchloride of mercury is commonly ordered as a mixture, from $\frac{1}{2}$ to $1\frac{1}{2}$ drachms of the liquor hydrarg. perchlor. (B.P.) being prescribed with some vegetable infusion. Iodide of potassium in the proportion of 5 to 20 grains to each ounce of the mixture is very commonly added, thus forming a biniodide of mercury with free iodide of potash. In Paris the perchloride is sometimes ordered in the form of a tabloid, with directions to dissolve it in coffee, wine or other drink which the patient may fancy.

The following plan of treatment has been drawn up, but cannot be considered to be a very efficient course. The preparation used as the standard is a pill containing 1 grain hydrarg. cum creta :—

	Months.	Pills.
First Course :—		
One month, taking 6 pills a day . .	1	180
Interval of 3 days without pills . .	—	—
One month, taking 4 pills a day . .	1	120
Interval of 7 days	—	—
One month, taking 3 pills a day . .	1	90
Interval of 1 month	1	—

	Months.	Pills.
Second Course :—		
Three months, taking 3 pills a day .	3	270
Interval of 1 month	1	—
Third Course :—		
Three months, taking 2 pills a day .	3	180
Interval of 1 month	1	—
Fourth Course :—		
Three months, taking 1 pill daily . .	3	90
Interval of 3 months	3	—
Fifth Course :—		
Three months, taking 1 pill daily . .	3	90
	21	1,020

Patients should be inspected once a week while under treatment, particular attention being paid to the mucous membranes of the mouth and tongue. The effect on each individual must be carefully watched, and the treatment varied to suit each case. After the third, fourth, and fifth courses, a short course of potassium iodide, 15–30 grains daily, may be administered with advantage.

Appendix IV

(*See page* 204)

PLAN OF TREATMENT, FOR TWO YEARS BY INUNCTION

	Months.	Grains Hg.
First Course :—		
42 daily inunctions	$1\frac{1}{2}$	840
Interval 3 months. See patient once a fortnight	3	—
Second Course :—		
42 daily inunctions	$1\frac{1}{2}$	840
Interval 3 months. See patient once a fortnight	3	—
Third Course :—		
30 daily inunctions	1	600
Interval 6 months. See patient once a fortnight	6	—
Fourth Course :—		
30 daily inunctions	1	600
Interval 6 months. See patient once a month if free from manifestations .	6	—
Fifth Course :—		
20 daily inunctions	$\frac{2}{3}$	400
	$23\frac{2}{3}$	3,280

The above scheme is suggested as a working plan for the ordinary case, and is to be modified as required to suit any particular individual.

Appendix V

(*See page* 209)

FORMULAE FOR CREAMS

Form "*O*" :—Mercury ʒi by weight.
Lanoline, ʒiv by weight.
Paraffin liq. Carbol, 2 per cent. } ad ʒx fluid.

10 minims of cream contain 1 grain of mercury.

At a temperature of 80°F. this cream separates, an oily layer equivalent to about a fourth of the bulk forming on the surface. At lower temperatures (50°F.) it is viscous and clumsy for use in a hypodermic syringe. It is too dilute, necessitating a bulky injection.

Form "*A*" :—Mercury, 2 parts by weight.
Lanoline, 3 parts by weight.
Paraffin liq. Carbol, 2 per cent. } ad 10 parts fluid.

1 grain of mercury in 5 minims.

This is a useful cream, which would be improved by omitting the carbolic acid. At temperatures up to 85°F. the globules of mercury sink but do not coalesce, stirring before use is all that is required. It is comfortably fluid at temperatures of 50°F. The strength is convenient for dosage purposes.

Form S 2 :—Mercury, 2 parts by weight.
Lanoline, 3 parts by weight.
Paraffin special to 10 fluid parts.

1 grain of mercury in 5 minims.

This appears to be a most useful formula, but would have to be tested practically.

PLANS OF TREATMENT BY INJECTION OF MERCURIAL CREAM

A. Each injection contains *one and a half* grains of metallic mercury.

	Months.	Grains Hg.
First Course :—		
6 injections, one each week	$1\frac{1}{2}$	9
Interval, 2 months	2	–
Second Course :—		
4 injections, one each fortnight . .	2	6
Interval, 4 months	4	–
Third Course :—		
4 injections, one each fortnight . .	2	6
Interval, 6 months	6	–
Fourth Course :—		
4 injections, one each month . . .	4	6
Total, 18 injections	$21\frac{1}{2}$	27

This plan was used for four years in Malta with satisfactory clinical results. The patient's serum reaction should be tested on three occasions at intervals of three, six and twelve months after the termination of the course. If the reaction is found to be positive on any of these occasions further courses must be ordered and the serum reaction again tested.

Plan B. Each injection contains *one* grain of metallic mercury.

	Weeks.	Grains Hg.
First Course :—		
9 injections, one each weekly . .	9	9
Interval, 6 weeks	6	–
Second Course :—		
6 injections, one each week . . .	6	6
Interval, 6 weeks	6	–
Third Course :—		
6 injections, one each week . . .	6	6
Interval, 8 weeks	8	–
Fourth Course :—		
6 injections, one each fortnight . .	12	6
Interval, 8 weeks	8	–
Fifth Course :—		
6 injections, one each fortnight . .	12	6
Interval, 8 weeks	8	–
Sixth Course :—		
6 injections, one each fortnight . .	12	6
Interval	12	–
Total, 39 injections	105	39

After the last interval the patient's serum reaction is to be tested; if it is negative no further treatment need be given, but after a further interval of twelve weeks the serum test is to be repeated. If the reaction is still negative, it should be tested again after a further interval of twenty-six weeks, when if it is found to be negative the patient may be regarded as cured. If, on any occasion, the reaction is found to be positive, one or more additional courses are to be given followed by a period of observation similar to the above.

LAMBKIN'S CALOMEL CREAM

Calomel ..	5	grammes.
Creo-Camph ..	20	c.c.
Palmitin basis to	100	c.c.

10 minims contain $\frac{1}{2}$ grain of Calomel. Melting point 37°C.

Appendix VI

(*See page* 219)

FORMULAE FOR ZITTMANN'S TREATMENT

The following formula gives sufficient for one patient for six to ten days :—

Bruised sarsaparilla root, 4 oz., is digested for 24 hours in 280 oz. of water.

To this the contents of No. 1 package are added, and the mixture boiled while the contents of No. 2 package, placed in a linen bag, are suspended in the vessel.

No. 1 package.—	Fennel seed Anise seed	Of each 80 grains.
	Liquorice root cut up Senna leaves	Of each 240 grains.
No. 2 package.—	Powdered alum Powdered white sugar	Of each 120 grains.
	Calomel, 80 grains.	
	Cinnabar, 20 grains.	

The mixture is kept just boiling till its bulk is reduced to a gallon. It is then strained through a fine cloth, and put up in bottles holding a little more than a pint. These are labelled Zittmann's Decoction No. 1 (Strong Dec.).

No. 3 package.—	Cardamom seeds Cinnamon bark Liquorice root	Of each, 60 grains.

The contents of No. 3 package are then added to the residue, together with 280 ounces of boiling water, and the whole is simmered down to a gallon. This is strained and bottled as before, and finally labelled No. 2 (Weak Decoction).

Pills R Hydrarg. subchlor., gr. 2.
Extract. colocynth., gr. 2.
Extract. hyoscyam., virid. gr. 2, make 2 pills.

The room must be kept at a temperature of 80°F.

The diet is not to contain sugar or spices.

The evening before the treatment is begun two pills are given. Next morning the patient has a light breakfast at 7 a.m. During the first four days, at 9, 10, 11 and 12 noon, the patient drinks half a pint of the strong decoction very hot. Smaller quantities may have to be used at first, as the mixture is rather nauseating.

Patient is kept in bed to sweat.

At 12.30 a light lunch is given, and at 3, 4, 5 and 6 p.m. a half-pint of the weak decoction cold.

The patient allowed up for an hour in the evening.

An alcohol rub or massage may be employed.

About 6 p.m. the patient has a good dinner, but without green vegetables. This routine is continued daily up to the fifth day, when the patient is allowed up and has a bath. On the same evening he has two more pills, and the next day the decoction as before, up to the fifteenth day. This finishes the treatment.

Appendix VII

(*See page* 260)

FORMULAE FOR USE IN GONORRHOEA

For Irrigation :—

(1) Potassium permanganate, gr. xx.
Distilled water, ℥ xx.

1 to 2 ounces to each pint of water.

(2) Albargin, gr. 50.
Distilled water, ℥ 20.

1 to 2 ounces to each pint of water.

(3) Nitrate of silver, gr. 20.
Distilled water, ℥ xx.

1 to 2 ounces to each pint of water.

(4) Sulphate of zinc, gr. 30.
Water, ℥ 20.

1 to 2 ounces to each pint of water.

For Injection :—

(1) Protargol, gr. 4.
Distilled water, ℥i

1 part to 3 of water to begin with, then equal parts of protargol solution and water, finally using the solution undiluted.

Occasionally the strength may be increased to 8 grains to the ounce for obstinate cases.

(2) Zinc permanganate 1 grain, distilled water 6 ounces; use with an equal quantity of warm water.

(3) Sulphate of zinc, 15 grains; subacetate of lead, 20 grains; tincture of opium and tincture of catechu, of each 2 drachms; water to 6 ounces. Dilute with at least an equal quantity of warm water to begin with.

(4) Ultzmann's injection. Zinc sulphate and powdered alum, of each 4 to 12 grains; liquid carbolic acid, 4 minims; water to 6 ounces.

(5) Zinc sulphate and zinc sulpho-carbolate, of each 1 grain; water, 1 ounce.

(6) Copper sulphate, $\frac{1}{4}$ grain; zinc sulphate, $\frac{1}{2}$ grain; water, 1 ounce; dilute with an equal quantity of warm water.

Appendix VIII

(*See page* 279)

FORMULAE FOR USE WITH SOFT CHANCRES

Wet Dressings :—

Boric acid, grs. 10 to the ounce.

Tr. iodi, m. 5 to m. 10 to the ounce.

Dilute nitric acid, B.P., m. 30 to the ounce.

Carbolic lotion, 1 in 40 to 1 in 60.

Formalin, m. 10 to m. 20 to the ounce.

Copper sulphate, grs. 10 to the ounce.

Zinc chloride, 2 to 5 grs. to the ounce.

Tr. benzoin co. applied undiluted.

Nitrate of silver, gr. 10 to the ounce.

Dry Applications :—Iodoform alone or mixed with an equal part of boric acid (freshly ground coffee is supposed to mask the objectionable smell).

Dermatol, a proprietary drug, is claimed to have the same effect as iodoform without the disagreeable smell.

A very good preparation is 1 part of salicylic acid, 2 parts of iodoform, and 5 of some neutral salt like zinc oxide or boric acid. Unna recommends 1 part of salicylic acid to 2 of iodoform ; this is, however, a somewhat irritating preparation.

If there is no suspicion of syphilis, black wash or calomel powder may be employed.

Appendix IX

REGISTERING ATTENDANCES (SYPHILIS)

Checking the attendances of men and entering up their treatment is always a troublesome matter. The following plan was found to answer satisfactorily at Malta.

In the case of men not yet diagnosed, the loose sheet is employed. In the first space the man's name and number, etc., are entered for identification purposes. In the second, the date on which the sore appeared together with any other suspicious symptoms while in hospital under treatment. The following squares are dated at the top, for whichever day of the week these men are inspected. When seen, the man's weight is entered, together with any note, such as " glands suspicious," to which the medical officer desires to have his attention drawn when next the man is seen. When the inspection has been concluded the man is told to come again in a week or fortnight according to circumstances, and in the square corresponding to this date an entry " Ob " is made. On any given day the medical officer only has to glance down the squares of this date to see who should attend on that particular day.

In the case of men on the register, a large book is ruled out as shown in the accompanying form, making the first two spaces, however, slightly larger. If more than one corps is treated, it saves confusion if the different corps are kept on separate pages. In the first square the man's name and number is entered, in the second space the following particulars are noted : Date on which treatment originally commenced, summary of treatment previous to any entry on this page, date of last manifestation of the disease. If this is done, a glance is sufficient to place the medical officer in

CORPS 4, R. BGDE. ROLL OF MEN ON SYPHILIS REGISTER. [SPECIMEN PAGE.]

Rank and Name.	Remarks.	January.				February.				April.		
	Began Treatment, etc.	5	12	19	26	2	9	16	23	2	9	
Pte. No. 652. Atkins, J.	1-5-05. Completed final course 1-12-06. Last signs, 2-10-05.	10.12.				Ob.						
Pte. No. 780. Smith, G.	1-6-06. 4 months pills; 6 injs. Muc. patches. 1-10-06.	No signs 9.10.		No signs 9.11		Inj.						
Pte. No. 213. Brown, C.	1-10-06. 20 inunctions, 1 month pills. Ulcer tonsil 10-12-06.	K.I. Ulcer tonsil Ag No_3 local. 10.0.	Omit K.I. Ulcer improved. No local 10.2.	K.I. Ulcer healed. No signs. 10.3.	Omit K.I. No signs. 10.2.	4 F. Begins course Injs. fortnightly. 10.3.		3 F.				

possession of the salient points in the man's syphilis history and to enable him, after examining the man, to determine at once what further treatment should be employed. In the succeeding squares the man's weight, treatment, any signs, etc., are entered, and on the date on which the man next attends the treatment then due to him is noted. At intervals, say once a quarter, the above particulars are entered in the man's syphilis sheet.

Syphilis Sheet

In this form the headings are arranged in order to give more room for practical details. The note on the nature of the sore has been dispensed with as affording no useful information ; the approximate time and place of infection are retained ; the latter is of some use as an indication of the local incidence of syphilis, while if the disease has been contracted for some months before treatment is commenced, relapses may be expected. A new station should be entered on the sheet. Treatment should be entered by courses, or months if no definite system of courses is adopted, as this greatly facilitates the work of summing up the treatment when a man is transferred to a new station.

SPECIMEN OF SYPHILIS CASE SHEET

SYPHILIS CASE SHEET

No., Rank and Name : 652, Pte. Smith, G. *Corps :* 4/R.B.
Station : Pembroke.
When and where contracted : London, Sept. 1906.
Malta *Register, Serial number* 13/06.
Placed on : 3/11/06. *Struck off :* ....
No. of months under treatment ....
Primary sore : Unknown. Did not report sick.
Lymphatic glands : General shotty enlargement.
Skin : Early macular syphilide on abdomen and back.
Mucous membranes : Superficial ulcer right tonsil. Early condylomata anus.
Other symptoms : Anaemia, nocturnal headaches.

Date.	Treatment.	Dose.	Progress.	Weight.	Urine.
3/11/06	Injection cream Hg. Local to ulcer and condylomata.	gr. 1½		10.0	Normal
10/11/06	Do. do. do.	gr. 1½	Ulcer tonsil healed condylomata gone.	10.2	
17/11/06	Injection cream Hg.	gr. 1½	Rash faded.	10.3	
24/11/06	Injection cream Hg.	gr. 1½	No signs.	10.3	
30/11/06	Injection cream Hg.	gr. 1½	,,	10.4	
1/12/06	Injection cream Hg. End of first course. Interval.	gr. 1½	,,	10.5	Normal
	Interval.				
15/12/06	No treatment.		No signs.	10.7	
29/12/06			,,	10.6	
12/1/07			,,	10.7	
26/1/07			,,	10.5	
	Begins 2nd course.				
9/2/06	Injection cream Hg.	gr. 1½	No signs.	10.6	Normal

No., Rank, Name.................... *Corps*.................... *Where and when contracted*......................
...... *Register, Serial No*....... *Placed on*.............. *Struck off*............... *Months under treatment*.....
Primary sore......................... *Lymphatics*......................... *Skin*.................
Mucous membranes......................... *Other symptoms*...

1st month. January, 1907. 5 weekly injections, cream gr. $1\frac{1}{2}$ each. Weight, Urine, Mucous patches on tongue, local treatment.	2nd month. February, 1907. 1 injection, cream gr. $1\frac{1}{2}$. K.I. one week. Weight, Tongue healed.	3rd month. March, 1907. Interval of non-treatment. No sign of syphilis. Weight, 31-3-07.	4th month. April, 1907. 2 injections, gr. $1\frac{1}{2}$ each. Urine normal. Weight,	5th month. May, 1907. 2 injections, gr. $1\frac{1}{2}$ each. Weight,	6th month. June, 1907. Interval of non-treatment. Weight,	Total for six months. 10 injs. gr. $1\frac{1}{2}$ each, K.I. one week.
7th month. July, 1907. Pills Hyd. e. Cret. gr. ij. each, twice daily. Weight,	8th month. August, 1907. K.I. for 21 days, 20 grs. daily. Omit Pil. Weight,	9th month. September, 1907. Pil. Hyd. e. Cret., gr. ij. twice daily. Weight.	10th month. October, 1907. Omit Pil. No treatment. Weight,	11th month. November, 1907. Pil. Hyd. e. Cret., gr. ij. twice daily. Weight,	12th month. December, 1907. No treatment. Weight,	Total for six months. 3 months pills. 1 month K.I.
January, 1908.	February, 1908.	March, 1908.	April, 1908.	May, 1908.	June, 1908.	Total for six months.

This is another form of suggested Syphilis Sheet based on the French Army plan. Each square is 2 in. square, and contains all necessary notes for the month's treatment and progress. Each half-year's treatment is summarized in the narrow column on the right. This plan would show at a glance how far the man had progressed in his treatment. The squares could be continued overleaf.—C. E. P.

Syphilis Record Book (A.B. 128)

Every alternate page of this book has the same headings as the syphilis case sheet. A short medical history of each case is entered in this book in order to preserve a permanent record of the case when the man and his syphilis case sheet are transferred to a new station.

Annual Return

A specimen of a suggested annual return is attached; this form gives as complete a summary of the incidence of syphilis during the year as it is possible to furnish.

SUMMARY OF THE TREATMENT OF SYPHILIS IN THE COMMAND (or . . . . DISTRICT) 190. .

	Mily. Hospl. Valetta.	Mily. Hospl. Cottonera.	Forrest Hospital.	Mily. Hospl. Imtarfa.	Total Malta.		Valetta.	Cottonera.	Forrest.	Imtarfa.	Total Malta.
No. of cases remaining on the Syphilis Register from 1905 .	21	14	31	6	72	No. of cases struck off the Register on completion of treatment in 1906	7	16	14	—	37
* No. of transfers received from other commands	2	31	11	2	46	* No. of cases transferred away from Malta, still under treatment	14	15	16	7	52
No. of men who were placed on the Register during 1906 . .	13	6	6	6	31	No. of cases remaining under treatment 31-12-06. . . .	34	19	2	5	60
No. of men who have been under treatment during the year or part of the year	36	51	48	14	149		55	50	32	12	149

Contracted in Malta, 27.

† No. of cases which have required admission while under treatment :—once, ... ; twice, ...

No. of cases which have relapsed after completing full course of treatment, ...

* Transfers between stations within the United Kingdom or within commands abroad are not to be shown in the line for transfers; this should only include transfers from or to abroad.

† Re-admissions only to be given in the case of men who have completed their full treatment and been struck off during the year.

Appendix X

RECORDING CASES (GONORRHOEA)

When ordering each day's treatment, it is important to know the condition of the urine on the previous day, as also the treatment then employed; when dealing with a large number of men it is impossible to remember the exact particulars of each case. The following plan has been found to answer satisfactorily in practice and to give all the necessary information. When the man is discharged, the number of days under treatment, complications, etc., can be entered up in tabular form for the purpose of compiling statistics. Quarter sheets of foolscap are hectographed as shown below; the ward orderly places these in order for the medical officer, the patients parade, and as their names are called they show their urine. The medical officer has the man's particulars in front of him, and can decide at a glance what treatment he wishes to adopt, the ward orderly, standing at his side, enters this up in his day book. By using abbreviations the writing can be much reduced.

GONORRHOEA SHEET

Name : 7251 Smith. 4/R.B. *No. of admission :* 1*st.* *Date of last one :* . . . .
Admitted : 1/1/07 *Discharged :* 20/1/07 *Days in hospital :* 20.
Condition on admission : Early acute anterior.
Relapse. . . . . *Days out of hospital*. . . . . *Complications* . . . .

Date.	1st Urine.	2nd Urine.	Treatment.	Remarks.
1/1/07	Cloudy.	Faint haze.	C.B. gr. j. P.I. gr. j. Cubebs.	Smear=Many Pcs. Gcs. in groups and free.
2/1/07	Less cloudy.	Clear.	Continue.	
4/1/07	Haze. M.	,,	A.B. $2\frac{1}{2}$. P.I. 2 grs. Cubebs.	
7/1/07	Clear. M.Th.	,,	C.B. gr. j. P.I. 4 grs. twice. ,,	
10/1/07	Clear. M. no Th.	,,	Omit C.B. P.I. 2 grs. twice. ,,	
12/1/07	Clear.	,,	,, P.I. 1 gr. ,,	
14/1/07	,,	,,	Omit all.	
16/1/07	,,	,,	,,	Beer 16th to 19th=4 days.
20/1/07	,,	,,	,,	

Abbreviations explained (similarly others may be used):—C.B. : Condy irrigation to bladder, strength in grains to the pint. A.B. : Albargin irrigation to bladder, strength in grains to the pint. C.I. : Condy injection to anterior urethra, strength in grains to the ounce. P.I. : Protargol injection to anterior urethra, strength in grains to the ounce. M. : Mucus. Th. : Threads. Pcs. : Pus cells. Gcs. : Gonococci. E.A. : Epididymitis on admission. E.T. : Epididymitis while under treatment.

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